Handbook of Cancer Survivorship

Michael Feuerstein

Editor

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To survivors around the world—
I hope this will help make all our lives a little bit easier.
Michael

Preface

It is quite remarkable that in so short a period we have seen cancer change from the stigmatized deep secret when no survivor dared to reveal it and complaints to physicians were met with "You should just be glad you are alive." Today, survivors of cancer—all 10 million of them—are eager to share their story with others and oncologists have a new interest in the care of their patients AFTER cancer. It is most worthwhile that Dr. Feuerstein has chosen to put together a baseline state of the art of the science of cancer survivorship, because it is new, still in its infancy and the research will likely explode in the next decade. There is much to be grateful for to pediatric oncology which has led the way and embraced survivorship long ahead of the adult oncology world. Many lessons learned there about clinical care, management of long-term side effects, prevalence of second malignancies, and the most effective models for follow-up should guide some of the early research in adult survivors.

Survivorship research is now represented by a whole field of investigators and clinicians devoted to improving the lot of the survivor from many different perspectives. Several are key contributors to this useful book. This handbook outlines the prevalence, burden, common problems, secondary prevention, and global perspective toward a new clinical entity that is the result of the cancer success story.

There are many important questions to be answered about survivorship and this book sets the stage for new researchers and clinicians entering the field. The reviews of the literature in each area will be invaluable as researchers move forward. I predict that this will serve as a foundation for the explosion of research that will be designed to assist in assuring that survivors are able to live their full lives to the fullest.

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Acknowledgments

Surviving cancer and living with the long-term consequences of the illness is not a simple process. While many survivors simply go on with their lives, still others experience episodic or persistent challenges that justify attention. Cancer is now often referred to as a "chronic illness." As many with chronic illnesses will tell you there are a set of challenges that often go along with living with an illness. That is what this book is all about. Providing the state of the scientific literature related to the burden of these problems, current understanding of the factors that impact these challenges and evidence-based approaches to help manage them is the focus of this book.

As a researcher and health care provider placed into the arena of cancer survivorship as a cancer survivor myself (malignant brain tumor), I noticed that there was no lack of information regarding cancer and its impact but as is often the case it was scattered across disciplines and journals. As I compiled information from many different fields and searched for a text book on the topic I noticed there were not many.

This Handbook covers topics from a number of diverse disciplines. The contributions from multiple disciplines provide a perspective often not found in one place even in the current zeitgeist of interdisciplinary approaches to chronic illnesses. Professional health care providers and researchers will benefit from such a perspective and through their efforts we can impact the quality of care and quality of life of cancer survivors. Each chapter was written by highly skilled scientists and clinicians. They are leaders in their respective fields from around the world. I would like to formally thank each one of these authors for their excellent work. Their ability to synthesize the literature from a clinically relevant perspective as well as generate suggestions for future research, practice, and/or policy is extraordinary. Their efforts will benefit thousands of us who receive more comprehensive, thoughtful care as a result.

I also want to thank my family. My wife Shelley and daughter Erica have lived with my preoccupation with this project. Thank you. My children, Sara and Andrew, son-in-law Umang and grandson Kiran provide a source of support for which I am forever grateful for. It is a joy to be part of their lives.

There are many in my professional and personal life who have provided me with much compassion. This has been the best medicine I could have had over the last few years and for that I am very thankful. My colleagues around the world have helped me move forward with my work and life. They know who they are and I would just like to say thank you. Your respect and willingness to continue to work with me means so much.

Since becoming a survivor myself I have met many other survivors at meetings, on the Internet, and in casual conversations. From talking with them it is clear there is a genuine need for a comprehensive public health approach to the challenges survivors face. Many in the public and private sectors are working toward that goal and their efforts need to be acknowledged. I also want to thank all the survivors I have encountered over the years in my roles as researcher, health care provider, and survivor. These individuals have clarified many of the subtleties involved in survivorship that often go unnoticed or are put on the back burner.

I would like to thank Jennifer A. Hansen and Karen A. Pescatore for their assistance with many aspects involved in the generation of this volume. I also want to thank Bill Tucker at Springer who believed in this project from the onset and has provided the necessary blend of professionalism, guidance, and independence. This could not have been accomplished without his support.

While survivors often say you "need to be there" to really fully understand the depths of these problems . . . this is clearly not the case. As thousands of professionals, family members and friends can attest, you don't need to have cancer to understand the nature of this illness and its potential impact on a person's or family's function, well-being and long-term physical health. Therefore, as health professionals, students of the health professions, families, friends, and policy makers we can all learn to play a critical role in helping to understand, solve, better manage, or share the many challenges and joys cancer survivor's face.

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Part I

Burden

Chapter 1

Cancer Survivorship

A Bird's Eye View from an Insider

Michael Feuerstein

As is now well known, the numbers of cancer survivors has increased considerably over the past decade and with aging trends in the population there is every reason to assume that this number will increase. Conditional survival rates, which provide a more dynamic prediction of survival for patients who have gone through initial treatment and continue to live several years post-diagnosis,[1,2] indicate higher votes of survival than convential data. This is great news for those afflicted with the illness and for their loved ones. It also provides positive evidence that innovative approaches for detection and management of these disorders are beginning to make a difference in saving lives. Yet, those who make it through the maze of detection, treatment, and management continue to experience problems. Often they are left to fend for themselves with these challenges. While much work has been done over the past decade to help those who have moved on to subsequent phases of living with cancer, there is much more that needs to be done. This handbook was developed with the intent of providing a foundation for health professionals from multiple disciplines to help improve their understanding and management of cancer survivors.

As with any clinical problem, not all survivors are the same. Each survivor has a complex array of potential risks, target problems, and potential long-term outcomes (Part I). The field is just beginning to understand this. We are faced with a major set of challenges that need to be addressed and addressed now. The traditional emphasis in public health has been to find commonalities and differences (e.g., genetic markers) in a problem, define its natural history, create effective surveillance systems, work toward identifying risk factors, and eradicating these through efforts to engineer the problem out of the system so that it no longer threatens the public health.[3] The management of cancer survivorship, while originating out of a clinical care model, can benefit from this public health orientation to research and practice. This has been recognized by a number of investigators and policy organizations and is beginning to emerge.[4] Hopefully, we will fully realize its potential in conjunction with cancer survivorship as another chronic illness. The topics covered in this book represent an effort in that direction.

Clinically, it is critical that we understand and address the concerns of the individual survivor presenting in our offices with persistent pain, recurrent bouts of fatigue, working memory deficits, emerging health risks or illnesses other than those related to cancer, and recurrence of tumor or metastases (Part II). These challenges need to be dealt with using evidence-based and timely approaches at a cost that is in line with patient and societal expectations (Part III). As approaches for these problems become more widely used in daily practice, access also needs to be considered. It is not enough to have these approaches available; they need to be available to all who need them. We also must adequately address psychosocial factors and biology from the perspective of diversity. Not because government tells us to or because there is funding for the topic, but because it is the right thing to do and it is logical if our goal is to help all.

The field of cancer survivorship is in its infancy. Both the clinical and public health approaches need to be pursued aggressively. The future is very bright in terms of our potential to prevent and/or manage these problems. Much work has been done over the years to create the conditions for such efforts. The work of pioneers who saw the need for such efforts years ago is gratefully acknowledged.[5,6] The chapters in this book highlight current knowledge and identify gaps in our understanding and management of critical challenges experienced by cancer survivors. Authors have also highlighted areas where additional efforts are warranted.

Much of what has been accomplished to date has been in the application of mental health concepts, theories, and treatments for problems that face survivors. The area of psychosocial oncology was developed to move these efforts forward and has been successful in doing so. This work continues its focus on understanding and assisting the cancer survivor within a "mental health perspective" using concepts from both conventional psychopathology and more recently, positive psychology[7] or efforts to learn more about harnessing well-being. Given that the field of cancer survivorship has a past in "psychosocial" approaches, it is not surprising that cancer survivorship is steeped in the behavioral health tradition. However, the widescale dissemination of the fruits of this labor, in addition to the fact that cancer survivors consistently face health system and societal challenges (e.g., reintegration into the workplace) which are related to health behavior in the broader sense, has not reached mainstream health care as yet. Also, reactions to individual hurdles that may actually represent adaptive responses to persistent or recurrent stressors faced rather than dimensions of "less severe" psychopathology have yet to be widely studied. Indeed, it was not too long ago that cancer was a death sentence. For some, this is still the case. However, we cannot abandon the approaches that have been so helpful in the past as we shift some of the focus on these more long-term survivors. Attention must also be given to understanding and improving our approaches to those in the advanced stages of cancer. Much has been accomplished in this area over the years and, from what survivors and families tell us, much more needs to be done. However, as more and more survivors are living full lives, old concepts of adaptation or adjustment are no longer appropriate. As survivors are living longer productive lives, there is a need for new concepts, measures, and interventions to maximize this outcome. Innovative models of cancer survivorship and care need to be advanced.

A recent survey by the Lance Armstrong Foundation discussed Chapter 2 indicates that despite all the "talk" about addressing the quality of cancer survivors' lives, survivors 2 years from diagnosis continue even experiencing behavioral health problems.[8] A chapter that addresses another prevalent aspect of burden covers the medical challenges faced by many survivors. Although the focus on quality of life continues to grow, the health care system in the United States as well as in other countries has not caught up with the understanding and approaches that can maximize the quality of health care available to help cancer survivors. While this situation is improving, as with other health problems, progress regarding access to needed services and approaches in this area are from ideal.

There are many other challenges that cancer survivors face that go beyond our current understanding. What can survivors, navigators, and providers tell us to help maximize optimal long-term health and create and maintain continuous communication and interaction with health care providers? (Part IV) What can be done about health disparities, the management of health risks over time requiring health behavior change, effective management of symptoms such as pain and emotional distress, workplace challenges, constructive use of social support and spirituality, existential concerns, and adaptation to advanced cancer? These are just some of the challenges survivors are confronted with. They are covered in this book.

As implied earlier, the field can also benefit from innovative models related to positive aspects of cancer survivorship. The chapter on a model of well-being was included as an example. State-of-the-art information regarding health behavior change (diet, activity, weight management, smoking, stress reduction) so important in optimal survivorship is also included. Consideration of prevalent symptom management of fatigue, pain, emotional distress, and relationships are also covered. Advanced cancer is not always covered in books on cancer survivorship. Chapters addressing adaptation, survivor, and provider perspectives of advanced cancer are covered to better inform research and practice in this area. Also, a chapter on survivors' view of quality care is included in the book. This is intended to give a voice to concerns that are often not heard as often as it needs to be given the exigencies of the moment. A chapter on approaches to cancer survivorship around the world was included to provide a perspective of the international arena Part (V). Lastly, I provide an overview of the field, some of my thinking in the area as scientist, provider, and survivor. In that final chapter I also present a challenge to us all Part (VI).

In June of 2002 after a life of excellent health and productivity I found myself in the quagmire called "cancer survivorship." I was diagnosed with a malignant inoperable brain tumor. After brain surgery for a biopsy, I found out that I had an anaplastic astrocytoma stage III in my right cerebellum moving into my pons. After 60 Gy of radiation and 12 months of chemotherapy, multiple MRIs indicated that the tumor was under control. The beast was tamed for now. I continue to receive MRIs every 4 months. I am one of the lucky ones; I can tell you about it. As you know, this type of tumor often takes the lives of many. While alive and I am certainly thankful for that, I have experienced many of the challenges covered in this book and continue to do so.

The motivation for me to compile this work which involved recruiting world renowned researchers and clinicians in diverse fields relevant to cancer survivorship was to provide you, the health professional and researcher, with a baseline of the "state of the art" regarding some of the more common challenges faced by cancer survivors. It is my hope that for those of you who treat patients this information will help you move survivors' care toward a more systematic evidence-based approach with an evolving long-term follow-up plan that considers not only the cancer, but general medical health and emotional, interpersonal, and lifestyle well-being. For those of you who are researchers, it is hoped that this volume gives you some pause to step back and think about how the questions you ask can better inform the scientific and healthcare communities in order to create and evaluate innovative approaches to prevention and management that truly represent a major improvement in existing efforts. For those involved in policy, there is a real need for society to evolve, to catch up to survivors, in order to better address their needs so that they can truly live the lives they deserve. We cannot ignore that as the population ages and the management of cancer becomes even more effective, prevalence is going to substantially increase. It is only a matter of time before these problems will be even more evident.

Cancer survivors have gone through a lot. We owe it to them to be more proactive. They should not have to endure financial concerns related to needed health care, access to limited quality health, unproductive efforts to find the "right" provider for a problem, limited access to long-term care insurance, financial strain due to lost income, and workplace problems including failures to obtain promotions, job loss, and inability to provide cancer-specific accommodations, to name but a few. Public policy needs to address these matters.

This handbook constitutes one more reminder that not all is well in this group. Yes, we are living and for that we are grateful. But much still needs to be done. Let's get on with it!

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Chapter 2

The Burden of Cancer Survivorship

A Pandemic of Treatment Success

Steven N. Wolff

1.0. INTRODUCTION

The life-altering burden of cancer has frame shifted from a narrow focus on the direct effects of anti-cancer therapy and overall survival to a spectrum of medical and nonmedical issues termed cancer survivorship. Survivorship still includes "traditional" consequences such as short- and long-term treatment side-effects and the development of second cancers.[1–3] In addition, cancer survivorship includes "newly" recognized psychological and psychosocial perturbations.[4–7] For many patients, the latter issues are more challenging than the defined course of direct anti-cancer therapy. These "new" responsibilities represent a formidable management challenge for physicians and the health care community.

Cancer medicine has become a paradigm of treatment success with the identification of causative factors, most notably genetic abnormalities, and the evolution of therapy from nonselective cytotoxic agents to biochemically defined targeted therapy. Currently, greater than 60% and 80%, respectively, of all adult and childhood cancer patients will survive more than 5 years after their initial diagnosis. Improved treatment, by eliminating debilitating toxicity and the inevitability of rapid demise, facilitated the realization that patients require the totality of survivorship care.

The medical literature notes that cancer patients suffer from the physical consequences of their disease, the adverse events from anti-cancer therapy, and the emotional toll than remain well after the completion of anti-cancer therapy.[8] This chapter will review the burden of cancer survivorship using a recently conducted cancer survivorship survey that elucidated areas of concern for patients. Data presented will also demonstrate that cancer survivorship is increasing and is a largely unmet responsibility of health care providers.

Reports of cancer survivorship needs and broad-based far-reaching recommendations have been presented by the National Institutes of Health Office for Cancer Survivorship, the Centers for Disease Control with the Lance Armstrong Foundation (LAF), and the Institutes of Medicine.[9–12] These proposals outline a plan for identifying, studying, and managing the spectrum of issues of cancer survivorship.

2.0. THE QUALITATIVE BURDEN OF CANCER SURVIVORSHIP FROM THE PATIENT'S PERSPECTIVE

To better understand the magnitude of the qualitative burden of cancer from the patient's perspective, the LAF conducted an open invitation Internet-based survey posted on the LAF Web site (http://www.laf.org). The survey was a large-scale battery of 83 queries about pathological and psychosocial topics such as medical support, emotional support, patient attitude, secondary health problems, financial issues, social relations, employment problems, and concerns about activities of daily living. From October 1–6, 2004, 1024 self-identified cancer patients responded and completed the survey. Demographics of the responders (shown in Table 1) indicated that most were Caucasian, married, college graduates, and living in or near a city. Ninety percent of responders had medical insurance and 57% had annual income greater than $50,000. Most of the responders were remote from cancer therapy with 73% more than 2 years from diagnosis and 45% as long-term survivors more than 5 years from diagnosis. Only 5% were recently diagnosed and 8% were undergoing cancer treatment. Whether this Internet-specific Web site study group was representative of the general population of cancer survivors remains undetermined and such bias must be considered in the application of results especially to underserved and minority populations with less access to health care resources.[13]

Table 2 illustrates the highlights of the survey. Almost half (47%) of the responders summarized that, "... in some strange way ... ", that dealing with their cancer diagnosis forced them to feel like they're leading a better life. A key observation from the survey was that nearly half (49%) of respondents have unmet "non-medical" needs. The burden of "non-medical" issues was apparent with more than half (53%) agreeing that the practical and emotional consequences of dealing with cancer were often harder than the medical issues. The cancer physician, although qualified as an oncologist, was identified as being unable to accommodate nonmedical needs. Among those who felt their nonmedical cancer needs were unmet, 70% said their oncologists did not offer any support in dealing with the nonmedical aspect of cancer. The other 30% said their oncologist was willing to talk about these issues, but did not have enough information or experience to assist in this area.

Inadequate availability of resources was a common thread. One third of the responders indicated that only limited resources were available to meet their emotional needs; 28% lacked resources for practical issues such as financial management and work-related issues; 23% lacked resources for physical issues. On the other hand, 86% of responders indicated that resources were available for medical issues directly related to the cancer. Family members and friends provided the bulk of support and were generally viewed as being the most important resource. More than 33% of responders indicated that government agencies were unable to provide support and 30% did not receive assistance from social workers. Twenty-four percent had not received assistance from their insurance company, 25% had some limited interactions,

Table 1. Demographics of the Cancer Survivorship Survey

Category	Result*
Sex (male:female)	50%:50%
Age (median year/range)	52 (18–>75)
Education (college graduate)	67%
Marital status (married)	68%
Type of residence	
A big city	20%
A suburb of a big city	33%
A smaller city	22%
A town or village	15%
A rural area or the country	10%
With health insurance	90%
Total family income	
<$30,000	15%
$30,000–$50,000	15%
$50,000–$100,000	31%
<$100,000	26%
Race/ethnicity	
White	89%
African American	2%
Hispanic	2%
Asian/Pacific Islander	3%
American Indian/Native American	1%
Other	2%
Timing of cancer diagnosis	
Less than 1 year prior to survey	12%
1–2 years prior to survey	14%
2–5 years prior to survey	28%
5–10 years prior to survey	21%
More than 10 years prior to survey	24%
Type of cancer	
Breast	20%
Prostate	16%
Melanoma	11%
Cervical	10%
Colon and rectal	7%
Ovarian/uterine/vaginal/vulvar	6%
Head and neck	5%
Lymphoma	5%
Thyroid cancers	3%
Testicular/penile	3%
Bladder	3%
Kidney	2%
Lung	2%
Leukemia	2%
Others	5%

*Percent of the 1020 responders (±3.1%) unless otherwise noted. Some categories may not sum to 100% due to declined responses.

and 34% received acceptable support noting that not all responders had access to insurance.

The emotional toll of cancer survivorship was substantial with 72% of respondents stating they had to deal with depression as a result of their cancer. Despite this, 78% did not seek out the services of a counselor, social worker, psychologist, or psychiatrist. The causation for not seeking assistance was not addressed in the study but

Table 2. Key Findings of the Survey

Category	Survey question	Result*
General health outcome	Currently experiencing "good health"	62%
	Optimistic that will die from something "besides cancer"	59%
	Life still affected by cancer ("more than a little")	40%
	Dealing with cancer made "life better"	47%
	Talk about cancer more than a few times/month	46%
Medical issues	Had to deal with chronic pain	54%
	Reduction or loss of sexual function	82%
	Secondary health issues caused or exacerbated by cancer	53%
Emotional needs	Emotional needs harder than physical needs	53%
	Suffered depression due to cancer	72%
	Problems with relationship with spouse/partner	60%
	Some/few/no resources available for emotional needs	33%
Nonmedical needs	Had unmet nonmedical cancer needs	49%
	Physician unable to assist with identified nonmedical issues	70%
Financial issues	Decreased income	83%
	Incurred financial debt due to cancer of >$25,000	9%
	Loss of insurance coverage	74%
	Turned down treatment option due to finances	12%
Survivorship	Would volunteer to assist in survivorship activities	70%

*% of category responders (±3.1%).

could be due to a lack of professional recognition or expertise compounded by a lack of available resources including health insurance coverage for these services. Sixty percent manifested problems in their relationship with a spouse or significant other.

Cancer survivorship issues remained long-term since 41% of survivors believed they would still die from cancer and 57% agreeing that cancer will always be a part of their life. Forty percent of responders stated that their lives were still consumed by cancer and related issues. Fear of recurrence from cancer remained active in 66% of survivors and another 20% had some concern. These results are profound considering that the majority of responders were remote from their cancer diagnosis and direct treatment. The survey also attempted to measure how often responders communicated with others about cancer. Ten percent indicated they had daily conversations about their cancer, 14% conversed weekly with the reminder communicating a few times per month (32%) or a few times per year (44%).

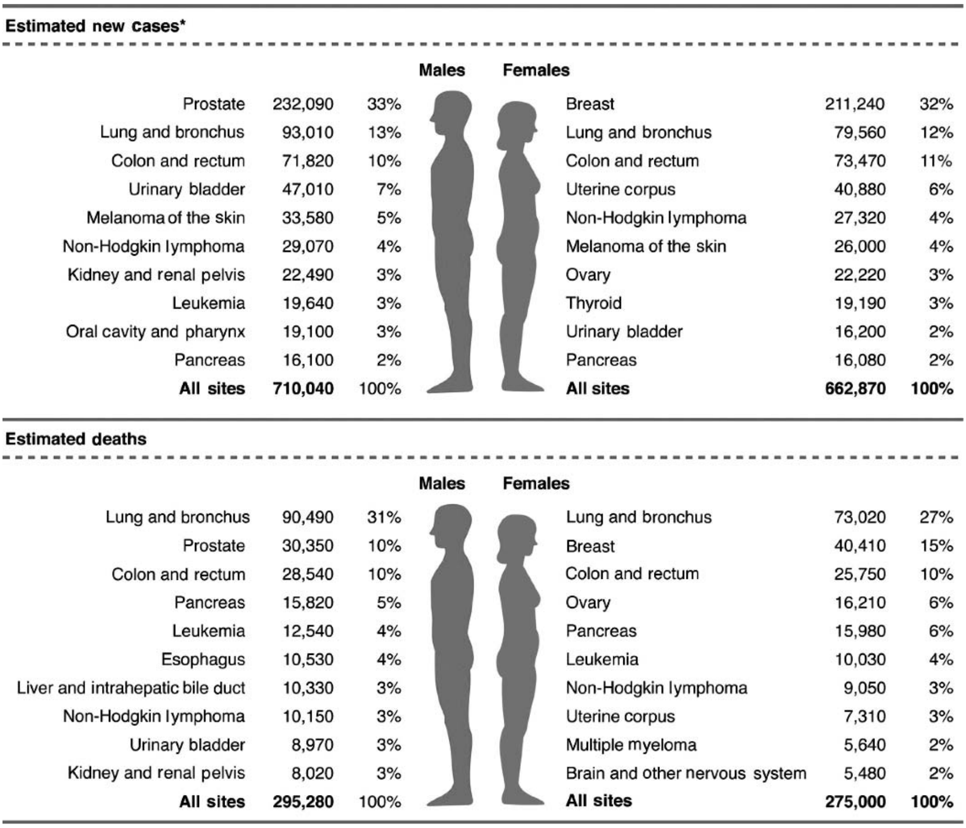
Well known secondary health problems, exacerbated by cancer treatment, remained important for more than half of respondents (53%) and within this group, 49% said they had a very difficult time dealing with the issue. Fifty-four percent of respondents had to deal with chronic pain. Thirty-three percent have dealt with infertility. Eighty-two percent had loss of sexual function.

Financial, insurance, and work-related issues were reported frequently in this survey noting that 43% said they've had to deal with decreased income as a result of their disease. Seventy-four percent had some loss of insurance coverage with 25% stating they went into debt as a result of their cancer and its consequences. For those in debt, 35% incurred debt up to $10,000, 24% of $10,000–$24,000, and 15% of $25,000–$49,000. Nine percent estimated their debt as greater than $100,000. Almost a third (32%) of respondents said they've had to deal with lack of advancement, demotion, or job loss as a result of their cancer and 34% said they felt trapped in their current job by the need to preserve health insurance coverage. Finally, 12% of respondents said they turned down a treatment option specifically because of financial concerns.

Despite these worrisome statistics, a remarkable aspect of the cancer survivor represented in this survey was their resilience and positive outcome from cancer. Sixty-two percent stated that they were in good health and 47% said, paradoxically, that dealing with cancer made life better. Also noted was 17% who indicated below average or poor health.

3.0. THE QUANTITATIVE BURDEN BASED ON CANCER STATISTICS

Understanding the burden of cancer survivorship also requires a quantitative appreciation of the incidence of cancer, the mortality of the disease, and the resulting number of accumulating survivors. The American Cancer Society publishes an annual summary of cancer statistics.[14] Based on data from the National Cancer Institute and mortality data from the National Center for Health Statistics, it is estimated that in the United States for 2005, a total of 1,372,910 new cancer cases and 570,280 deaths are expected. Since 1999, cancer has surpassed heart disease as the leading cause of death for persons younger than 85 years. The estimated number of cancer cases in 2005 and the death rate, by various cancer sites, are shown in Figure 1, demonstrating which cancers are most common in incidence and those with the highest mortality.[14] The incidence of prostate, lung, and colorectal cancer for men



Estimated new cases*

Males			Females		
Prostate	232,090	33%	Breast	211,240	32%
Lung and bronchus	93,010	13%	Lung and bronchus	79,560	12%
Colon and rectum	71,820	10%	Colon and rectum	73,470	11%
Urinary bladder	47,010	7%	Uterine corpus	40,880	6%
Melanoma of the skin	33,580	5%	Non-Hodgkin lymphoma	27,320	4%
Non-Hodgkin lymphoma	29,070	4%	Melanoma of the skin	26,000	4%
Kidney and renal pelvis	22,490	3%	Ovary	22,220	3%
Leukemia	19,640	3%	Thyroid	19,190	3%
Oral cavity and pharynx	19,100	3%	Urinary bladder	16,200	2%
Pancreas	16,100	2%	Pancreas	16,080	2%
All sites	**710,040**	100%	**All sites**	**662,870**	**100%**

Estimated deaths

Males			Females		
Lung and bronchus	90,490	31%	Lung and bronchus	73,020	27%
Prostate	30,350	10%	Breast	40,410	15%
Colon and rectum	28,540	10%	Colon and rectum	25,750	10%
Pancreas	15,820	5%	Ovary	16,210	6%
Leukemia	12,540	4%	Pancreas	15,980	6%
Esophagus	10,530	4%	Leukemia	10,030	4%
Liver and intrahepatic bile duct	10,330	3%	Non-Hodgkin lymphoma	9,050	3%
Non-Hodgkin lymphoma	10,150	3%	Uterine corpus	7,310	3%
Urinary bladder	8,970	3%	Multiple myeloma	5,640	2%
Kidney and renal pelvis	8,020	3%	Brain and other nervous system	5,480	2%
All sites	**295,280**	100%	**All sites**	**275,000**	**100%**

Figure 1. Cancer Cases and Death by Sex in 2005 for the 10 Leading Causes of Cancer. (Adapted from Ref. 14)

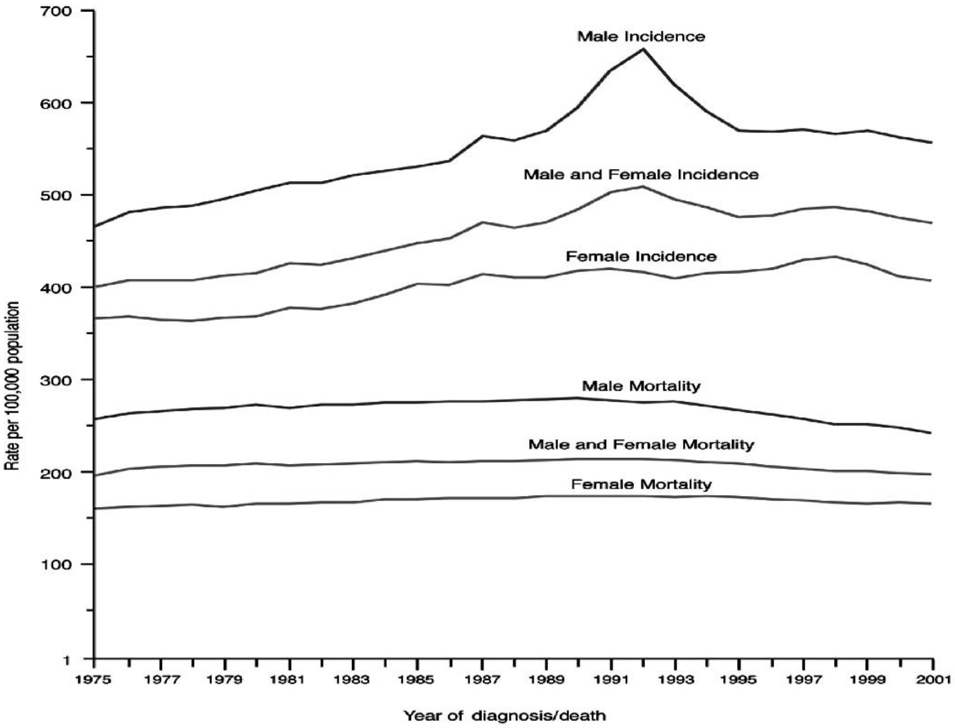


Figure 2. Annual Age-Adjusted Cancer Incidence and Death Rate for All Sites by Sex in the United States from 1975 to 2001. (Adapted from Ref. 14)

and breast, lung, and colorectal cancer for women are by far the most frequent. These sites of disease also represent those with the highest mortality. Data based on tumor type and site are important because each can be associated with variable consequences based on the organ dysfunction, treatment adverse events, and long-term effects.

Figure 2 demonstrates graphically the annual age-adjusted cancer incidence and death rates from 1975 to 2001 noting substantial increase in incidence for the past two decades with a recent trend for decline.[15] From 1993 through 2001, the overall annual cancer mortality rate fell by an average of 1.1% a year due to better screening, reduction in smoking in men and improved cancer therapy.

Treatment success and survival rates, similar to incidence, are heterogeneous when calculated for specific cancer site. For selected cancers, the annual age-adjusted cancer incidence rate for men and women are shown in Figure 3.[14] As noted, for the two most common cancers, prostate cancer in men and breast cancer in women, the incidence continues to substantially increase. The age-adjusted death rates for various cancers are shown in Figures 4 and 5 for women and men respectively.[14] As noted, the death rate for the common cancers, breast, colorectal, stomach, and prostate cancer are in decline. Remarkably, the death rate for lung cancer in men is also in decline leading to the overall diminished cancer mortality; unfortunately, a similar decline has not yet been observed for women.

The National Cancer Institute and the Centers for Disease Control, using the 1971 to 2001 incidence and death rate for the various cancers, estimated the number of persons living with cancer.[16] As shown in Figure 6, the number of patients in the

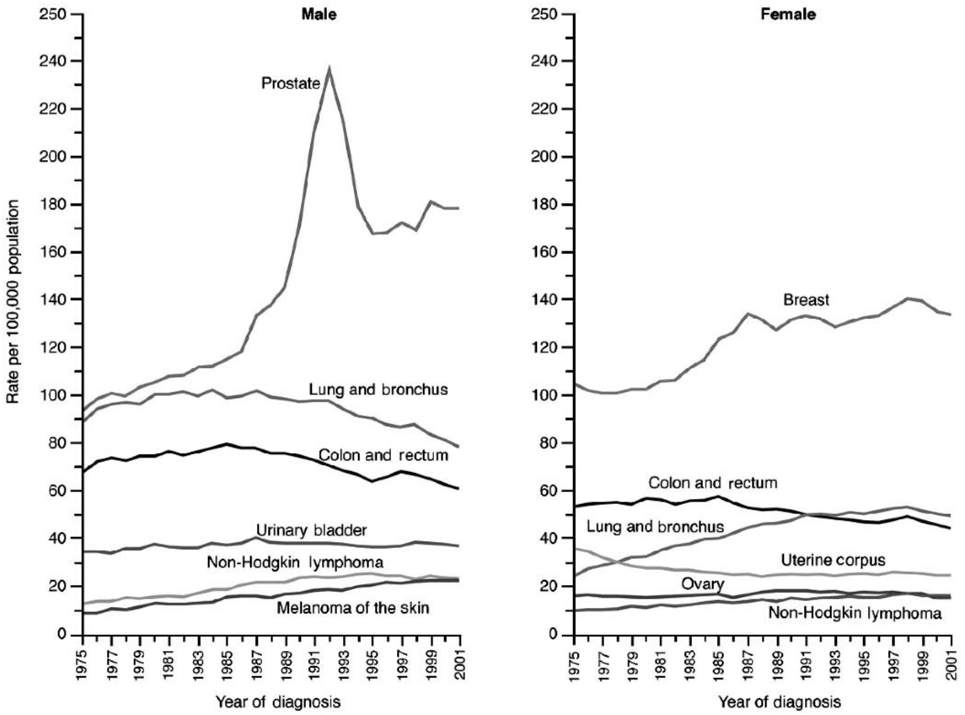


Figure 3. Annual Age-Adjusted Cancer Incidence Rate by Sex for Selected Cancer Types in the United States from 1975 to 2001. (Adapted from Ref. 14)

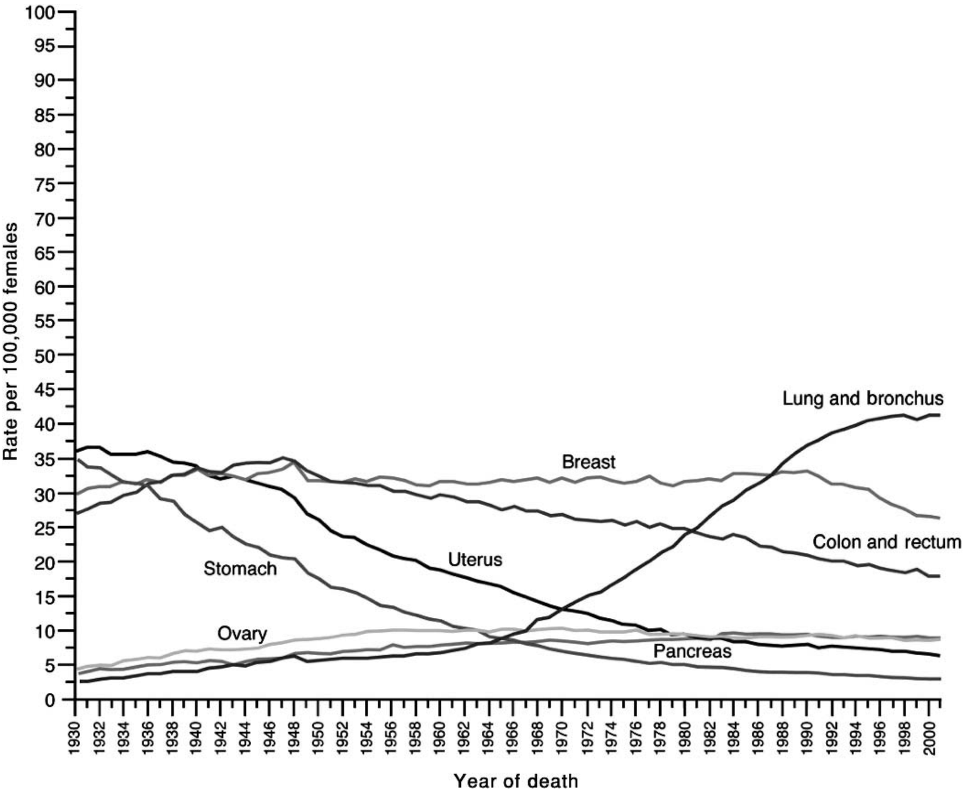


Figure 4. Annual Age-Adjusted Cancer Death Rate for Females for Selected Cancer in the United States from 1930 to 2001. (Adapted from Ref. 14)

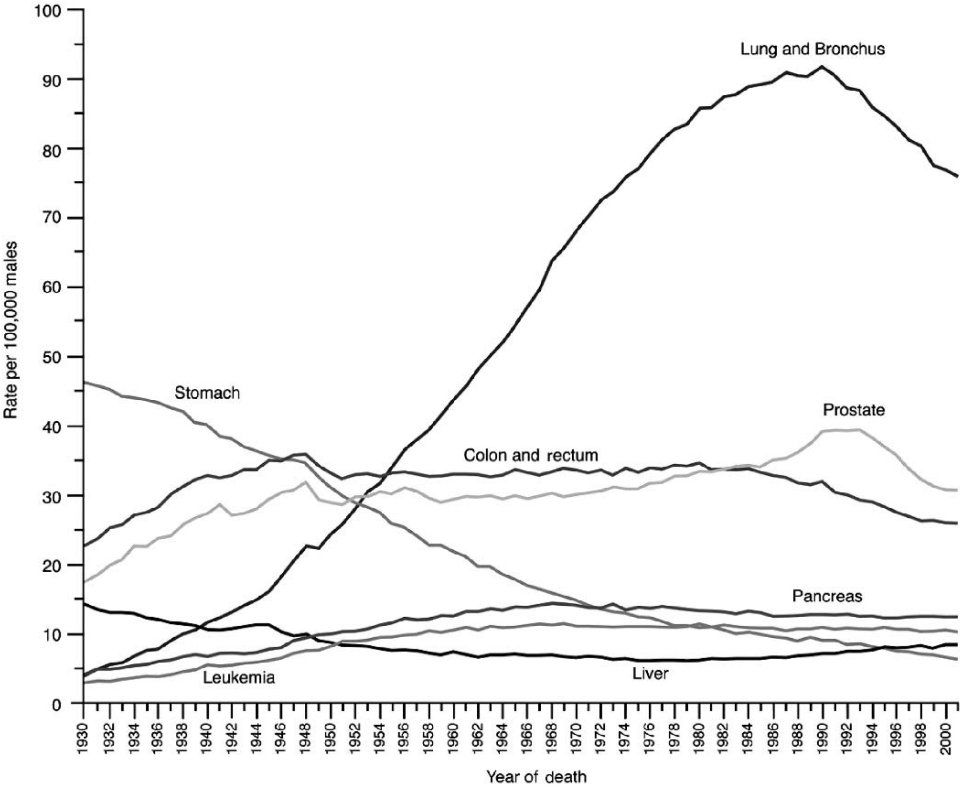


Figure 5. Annual Age-Adjusted Cancer Death Rate for Males for Selected Cancer in the United States from 1930 to 2001. (Adapted from Ref. 14)

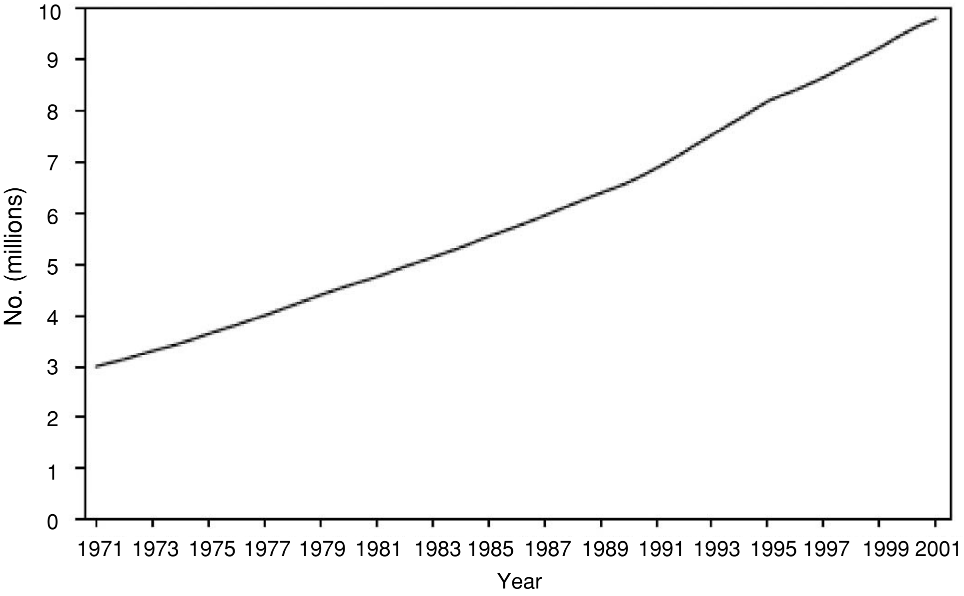


Figure 6. Estimated Number of Living Persons Who Have Ever Received a Diagnosis of Cancer in the United States by Year from 1971 to 2001. (Adapted from Ref. 16)

United States ever diagnosed with cancer increased from 3.0 million (1.5% of the U.S. population) in 1971 to 9.8 million (3.5% of the U.S. population) in 2001. For 2001, an estimated 14% of these survivors had their cancer diagnosed at least 20 years previously. Worldwide, it is estimated that more than 25 million people are alive with a diagnosis of cancer.[17] Adults are the preponderance of these survivors since childhood cancers (those diagnosed among children under the age of 15) account for less than 1% of all cancers diagnosed. It is estimated that more than 60% of all cancer survivors are greater than 65 years of age with less than 1% younger than 19 years of age.[18] However, the overall success for the treatment of childhood cancer will lead to an increasing accumulation of young adults as survivors of childhood cancer. In adults, the preponderance of survivors are those with the most common neoplasms such as breast, prostate, and colorectal cancer.[18] These data forecast that the number of patients with a diagnosis of cancer will continue to increase with the increasing cancer incidence in our enlarging aging population along with the further refinement of cancer therapy. It is understandable how the quantitative burden of cancer survivorship is currently substantial and anticipated to increase in the future.

4.0. DISCUSSION

The results of the LAF survey presented in this chapter are consistent with those of similar surveys that demonstrated the broad-based burden of cancer survivorship, the many serious and long-term issues, and inadequate resources for assisting patients especially for "non-medical" needs.[6,19] These studies also demonstrated the perseverance of the cancer patient to overcome those hardships with many survivors paradoxically experiencing that their life was actually improved by cancer. Learning how patients manage could lead to insightful avenues for cancer survivorship activities through positive psychology interventions.[20]

The National Health Interview Survey of 1992 demonstrated that most (58%) cancer survivors had received some patient educational materials from a health care provider.[19] However, relatively few had received counseling or participated in support groups (14.2%), contacted cancer organizations after their diagnosis (10.9%), or participated in a research study or clinical trial as part of their cancer treatment (4.7%). One ninth (10.7%) of the survivors were denied health or life insurance coverage because of their cancer. Nearly one fifth (18.2%) of the cancer survivors, who worked before or after their cancer was diagnosed, experienced employment problems because of their cancer. Specific data in breast cancer survivors demonstrated that 16% were unable to obtain life insurance and 7% lost health insurance as a result of a diagnosis of breast cancer.[6] Analysis of large cancer centers also suggested that many resources were not readily available such as school reentry programs (19% of cancer centers), nutrition counseling (14% of cancer centers), and counseling addressing fertility and sexual concerns (14% of cancer centers).[21] These inadequacies would likely be more frequent in smaller programs. Overall, these studies demonstrated that there were substantial degrees of unmet needs for cancer survivors.

However, samples of breast cancer survivors have demonstrated less profound cancer impact.[22] As noted, breast cancer survivors may have a quality of life as good as or better than age-matched control women.[23] Similar rates of sexual dysfunction are seen between breast cancer survivors and postmenopausal women who have not had cancer.[24] Marital breakdown was no more common among women after breast cancer than among control women matched on demographics.[25,26] There may be no major differences in quality of life between women having undergone a mastectomy compared to those having breast conserving surgery.[27] Other studies also suggest that only a minority of patients have significant psychological distress. For example, older adult long-term cancer survivors do not demonstrate clinical levels of posttraumatic stress disorder although over 25% have clinical depression or display important symptoms of psychological distress related to the continuing effects of cancer and its treatment.[28]

Similarly, the variability of the impact of cancer upon the diagnosis of depression is discussed in a review paper in which the prevalence ranges from slightly greater than the normal population (6–15%) to suggesting that more than one third of all cancer patients were depressed and were under-diagnosed and under-treated based primarily on the belief that cancer patients should be depressed.[29]

Reconciliation of these apparent contradictions suggests that many survivors will overcome the challenges related to their disease and that with better understanding and treatment even more would do so. Survivorship issues may also be related to disease specifics or resolved with resources targeted to these specialized circumstances. Overall, more exacting evaluation of cancer survivorship issues is still required and analysis of those who successfully manage their cancer burden may give insight into useful mechanisms of cancer survivorship.

A limitation of the LAF survey and others presented in the literature is selection bias and the substantial under representation of nonmainstream and especially underserved populations.[13] It is conceivable that in these populations, other not yet identified issues of survivorship with more problematic outcomes would be noted.[30] It has been well established that cancer health outcome disparity exists for these populations who generally may present in more advanced stages of their disease, may not receive exemplary therapy, manifest greater toxicity from therapy, and demonstrate poorer overall survival.[31,32] It is therefore likely that nonmedical survivorship issues would be even more problematic considering the social injustice, such as the lack of private health insurance, in these underserved populations. Evaluation of the impact of ethnicity, culture, and access to health care is required for the complete understanding of the burden of cancer survivorship.

Currently, it is estimated that the annual monetary health care expenditures for cancer in the United States is approximately 65 billion dollars of which only a small proportion is allocated to nonmedical issues of cancer survivorship. The totality of the economic burden for the cancer patient has not been fully measured, especially when job-related issues that affect adults in the prime of their employment are considered.[33] How to provide for “non-medical” survivorship management when the “medical” aspect of health care is singularly financially challenging is an issue that must be addressed.

5.0. CONCLUSIONS

Quantitatively, cancer will directly affect one in three persons and 25% of all families including 20% of parents who will be cancer survivors caring for children. Cancer is now the major cause for death in patients less than 85 years of age. Qualitatively, the burden of cancer transcends all medical disciplines especially impacting the emotional well-being of many survivors. As a potentially fatal illness with a continued fear of relapse, the burden of cancer remains chronically active well beyond the period of first diagnosis and active cancer therapy. For many patients, the emotional challenges of cancer survivorship are more profound and have fewer resources for mitigation compared to medical issues.

The cancer patient and their community face many medical and nonmedical challenges of cancer survivorship. As cancer therapy continues to improve, survivorship will become even more important leading to the pandemic of cancer survivorship. Urgently required are additional investment into research resources for better understanding, training of health care personnel, and provision for the complete management of both medical and nonmedical issues of cancer survivorship.[34]

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Chapter 3

Quality of Care

Craig C. Earle

1.0. INTRODUCTION

In its recent report,[1] the Institute of Medicine (IOM) urged as its first recommendation that cancer survivorship be recognized as "a distinct phase of cancer care." The rationale for this is that until recently cancer survivorship has been relatively neglected in clinical practice, advocacy, and research. By virtue of their sheer numbers and the expected rate of growth of this population, however, the quality of the medical care cancer survivors receive is an increasingly important public health issue. Part of the problem is that there has not been a unifying identity for these patients and the challenges they face. The IOM report strove to address this by defining and highlighting a constellation of long-term and late effects that result from having had cancer treatment: issues around surveillance for and prevention of recurrence and second cancers, long-term and late effects of treatment, psychological sequelae, and social problems such as employment and insurance concerns.

Many define a cancer survivor as anyone with a diagnosis of cancer who is still alive. For the purposes of this chapter, however, we will limit the discussion to those aspects of care relevant to the patient who has completed primary therapy for cancer and is currently free of disease, no matter how soon after completion of treatment. The specific problems survivors encounter vary widely from person to person. As a result, it is not possible to define exactly what quality medical care is for a typical survivor. Rather, quality survivor care is rooted in patients having a plan for survivorship. Knowing what was done, what will be done, and who will do it is in many ways more important than the specifics of the recommended plan. The chapter will give an overview of the medical issues adult survivors of cancer may have to deal with as a result of their disease and/or its treatment and will discuss the elements of quality survivor care, organized around the IOM's recommended "survivorship care plan" (Table 1).

Table 1. The Institute of Medicine Survivorship Care Plan

Upon discharge from cancer treatment, including treatment of recurrences, every patient should be given a record of all care received and important disease characteristics. This should include, at a minimum:

1) Diagnostic tests performed and results
2) Tumor characteristics [e.g., site(s), stage and grade, hormone receptor status, marker information]
3) Dates of treatment initiation and completion
4) Surgery, chemotherapy, radiotherapy, transplant, hormonal therapy, or gene or other therapies provided, including agents used, treatment regimen, total dosage, identifying number and title of clinical trials (if any), indicators of treatment response, and toxicities experienced during treatment
5) Psychosocial, nutritional, and other supportive services provided
6) Full contact information on treating institutions and key individual providers
7) Identification of a key point of contact and coordinator of continuing care

Upon discharge from cancer treatment, every patient and his/her primary health care provider should receive a written follow-up care plan incorporating available evidence-based standards of care. This should include, at a minimum:

1) The likely course of recovery from acute treatment toxicities, as well as the need for ongoing health maintenance or adjuvant therapy
2) A description of recommended cancer screening and other periodic testing and examinations, and the schedule on which they should be performed (and who should provide them)
3) Information on possible late and long-term effects of treatment and symptoms of such effects
4) Information on possible signs of recurrence and second tumors
5) Information on the possible effects of cancer on marital/partner relationship, sexual functioning, work, and parenting, and the potential future need for psychosocial support
6) Information on the potential insurance, employment, and financial consequences of cancer and, as necessary, referral to counseling, legal aid, and financial assistance
7) Specific recommendations for healthy behaviors (e.g., diet, exercise, healthy weight, sunscreen use, immunizations, smoking cessation, osteoporosis prevention). When appropriate, recommendations that first-degree relatives be informed about their increased risk and the need for cancer screening (e.g., breast cancer, colorectal cancer, prostate cancer)
8) As appropriate, information on genetic counseling and testing to identify high- risk individuals who could benefit from more comprehensive cancer surveillance, chemoprevention, or risk-reducing surgery
9) As appropriate, information on known effective chemoprevention strategies for secondary prevention (e.g., tamoxifen in women at high risk for breast cancer; aspirin for colorectal cancer prevention)
10) Referrals to specific follow-up care providers (e.g., rehabilitation, fertility, psychology), support groups, and/or the patient's primary care provider
11) A listing of cancer-related resources and information (e.g., Internet-based sources and telephone listings for major cancer support organizations)

Source: IOM Report: "From Cancer patient to Cancer Survivor: Lost in Transition," Box 3–16, pp. 152–3, Adapted from the President's Cancer Panel (2004).

2.0. MANAGING THE TRANSITION FROM CANCER PATIENT TO CANCER SURVIVOR

The first step in managing a successful transition from cancer patient to cancer survivor is to ensure that the patient and all involved providers know the patient's diagnosis, treatments received, and plan going forward. The goal is to optimize both the continuity and coordination of care. Cancer patients often require treatment from multiple providers: surgeons, medical oncologists, radiation oncologists, nutritionists, and psychosocial providers, who may all work in separate sites. And these providers may be separate yet again from their primary care providers (PCPs). Such a situation is ripe for fragmented, uncoordinated care that can lead to both underuse and overuse of services. Advocacy organizations such as the American Cancer Society and the Lance Armstrong Foundation have tried to help survivors become more informed by providing information on survivorship issues for common cancer types and helping survivors summarize their medical treatment and plan for follow-up care. The IOM recommends that it is incumbent on health care providers, however, to become more proactive in assisting patients make the transition from cancer patient to cancer survivor.

Because of the current inconsistency in the quality of survivorship care, the second recommendation of the IOM report offered a strategy for improving the ongoing clinical management of cancer survivors. It stated that "patients completing primary treatment should be provided with a comprehensive care plan summary and follow-up care plan that is clearly and effectively explained. The 'Survivorship Care Plan' should be written by the principal provider(s) who coordinated oncology treatment." This would commonly, but not always, be done by the medical oncologist if one was involved. The idea of a formal, written plan is not a new one, but it is not currently widely used in practice. Practical barriers to the creation of such a document are discussed later in this chapter. Regardless of whether it is achieved formally or informally, though, ensuring clarity about the plan going forward among all parties involved is imperative.

3.0. TREATMENT SUMMARY

The first aspect of the survivorship care plan is the treatment summary. Patients vary widely in knowledge about their diagnosis and the treatment they received.[2] Surgeons describe their procedures in operative reports, and radiation oncologists almost uniformly write "completion notes" that summarize the site, indication, and dose and fractionation of the radiation that was delivered. Medical oncologists do not consistently summarize a course of their treatment, however. Part of the reason is that systemic therapy is generally an ongoing process rather than a discrete treatment event or course. Doses of drugs are reduced and reescalated, breaks are taken, and the duration of therapy varies depending on the clinical situation, tolerance of treatment, and tumor response. The IOM's recommended care plan suggests that "upon discharge from cancer treatment, including treatment of recurrences, every patient should be given a record of all care received and important disease characteristics." Such a treatment summary would indicate the diagnosis and stage, the name of the regimen and component drugs, and starting dosages. It would indicate the number of cycles, the finishing doses, the toxicities that necessitated any dose delays or reductions, the best response, and the reason treatment was discontinued. Awareness of these elements of the patient's history is necessary to guide surveillance for recurrence and late effects.

4.0. ONGOING CARE PLAN

The follow-up care plan should include communication about the likely course of recovery from acute treatment toxicities, as well as the need for ongoing health maintenance or adjuvant therapy. For example, any recommended chemopreventive strategies, such as tamoxifen for breast cancer or aspirin for colorectal cancer, should be reviewed at this time. It should also lay out the plan for surveillance for recurrence or development of new cancers. It should acknowledge the common late effects of treatment that need to be watched for, and identify which providers will be responsible for ongoing cancer monitoring, non-cancer care, and who to contact for psychosocial and supportive issues that may arise. Explicit identification of providers is important not just to optimize coordination of care in order to avoid unnecessary use of resources, but also to ensure that care doesn't fall through the cracks due to unclear expectations around which provider will do what. It is important that the survivorship care plan not be static, however. It may need revision as new knowledge about late effects (e.g., recognition of stroke as a complication of chemotherapy[3]), genetic predisposition (e.g., the association between BRCA2 and pancreatic cancer), or surveillance recommendations (e.g., the change in American Society of Clinical Oncology's (ASCO) recommendations for the follow-up of colorectal cancer[4]) comes to light.

An important principle for ongoing care is that it should be tailored to the patient's clinical situation and preferences. Some patients cured with a simple surgical excision of an early-stage colon cancer may be able to move on with their lives with little long-term physical or psychological concern. Others in the same situation may have devastating symptoms or distress. Some patients may prefer not to think about their cancer and opt for the minimum recommended follow-up, while others are so concerned that they run the risk of having their lives defined by survivorship and need to be encouraged to shift focus away from their cancer history. No two patients are in the same clinical situation or share exactly the same values. As a result, in order to achieve optimum follow-up care, a patient-centered approach is needed.

4.1. Guidelines for Survivorship Care

Ideally, the survivorship care plan would be organized around a set of widely agreed-upon clinical practice guidelines. Guidelines are best when they are based on evidence and derived in a formal process of either evidence evaluation and/or consensus. Unfortunately, there are few guidelines available for the management of cancer survivors. This situation reflects a lack of high-quality evidence in most cases, particularly for survivors of less-common cancers. In addition, experts widely disagree on recommendations.[5] Most guidelines that do exist focus only on issues of surveillance.[4,6,7] Consequently, the third recommendation of the IOM report is for the refinement of existing clinical practice guidelines to include survivorship care, and calls for the development of new evidence-based guidelines through public- and private-sector efforts.

Guidelines can still be useful even when based more on consensus than evidence, however. Clinical practice guidelines can decrease variation in care, particularly overuse of investigations[8] that can lead to inefficiencies in health care delivery. For example, breast cancer guidelines recommend against imaging studies and tumor markers to look for metastases,[6,7] and colorectal surveillance guidelines caution against the overuse of nonspecific blood work.[4] In addition to economic costs, overused surveillance tests and visits often lead to false positive results and further investigations, with inherent physical and psychological risk.[9,10] Indeed, randomized trials have not been able to consistently find positive psychological effects associated with surveillance.[10,11] While being told that there is no sign of cancer recurrence can understandably decrease anxiety,[12] the stress leading up to it, inconvenience and often discomfort of testing, and not infrequent detection of incidental abnormalities are instances in which surveillance causes harm.[13,14] False positive results cause mental anguish and usually lead to further tests, possibly invasive ones like biopsy, that add expense and can lead to other complications.

While they may limit unnecessary care, guidelines can also facilitate the delivery of necessary care, as payers increasingly look to guidelines to make reimbursement decisions. If clinicians can agree that a certain procedure is beneficial and codify it in a guideline, it is difficult for an insurer to deny coverage for it. The most comprehensive guidelines for monitoring long-term and late effects of cancer therapy have been developed by the Children's Oncology Group (http://www.survivorshipguidelines.org). They have developed guidelines for the surveillance of long-term and late effects of pediatric cancer patients that are based on evidence where it exists, and consensus where it does not. Many of the recommendations they make are applicable to adult cancer survivors as well.

4.1.1. Surveillance for Cancer Recurrence

Surveillance for recurrence of cancer is usually the first thing that comes to mind when survivor care is discussed. However, assessing the quality of surveillance care is not easy. Surveillance is something that seems like an obvious good thing. Patients like the notion because after completing a regimented treatment program, many are reassured by the ongoing tasks of surveillance and resultant contact with their providers.[11] Oncologists also like the opportunity to provide reassurance.[15]

The main reason for surveillance is to detect local or distant disease at a time when survival can be prolonged by interventions to either cure the disease or at least treat it more effectively than when it is discovered later. Surveillance strategies generally consist of some combination of office visits with history and physical examination, blood work including tumor markers, imaging studies, and examination of the site of the original cancer. Surveillance of the primary tumor site can in some cases detect salvageable local recurrences, for example, in anal, breast, and head and neck malignancies. Other times, like in colon cancer, the rationale is more to detect new primaries in an organ presumed to have a predisposition. For disease that has spread beyond the primary site, there are some cancers, like colon cancer, renal cell carcinoma, and some sarcomas in which a small proportion of patients who recur distantly with oligometastatic disease can undergo surgery for possible cure.[16]

In many situations, however, there is not even a plausible rationale to intensely monitor asymptomatic patients in order to find incurable distant recurrence. Conventional wisdom is that if cancer is caught early it can be cured, but unfortunately the same is usually not true of early detection of metastatic cancer. Second-look surgeries to detect recurrence of ovarian and pancreatic cancers have not been associated with improved outcomes because such recurrences are generally not curable.[17] Moreover, early institution of palliative chemotherapy in asymptomatic patients does not appear to provide benefit in most situations.[11,18] Detecting and preventing potentially catastrophic complications of recurrence like spinal cord compression and pathological fracture has been put forth as a rationale for surveillance in situations in which recurrences will always be incurable, but randomized trials have not been able to detect a benefit from this.[19]

The use of imaging studies is often the most controversial aspect of surveillance because such scans are relatively expensive and are usually only able to find distant, incurable recurrences. Even in examples in which there is a strong rationale for them because of effective salvage therapies that are clearly more effective when the tumor burden is low, the majority of relapses present with signs, symptoms, or abnormalities on blood work (e.g., elevated LDH in lymphoma) without needing scans.[20]

Table 2. ASCO Breast Cancer Surveillance Guidelines[7]

- Monthly breast self-examination
- History and physical examination every 3–6 months for 3 years, then every 6–12 months for 2 years, then annually
- Annual mammography of the preserved and contralateral breast

Data are not sufficient to recommend routine bone scans, chest radiographs, hematologic blood counts, tumor markers (carcinoembryonic antigen, cancer antigen [CA] 15-5, and CA27.29), liver ultrasonograms, or computed tomography scans.

Surveillance involves upfront costs for a future, uncertain benefit. These costs can be quite substantial. One estimate of average 5-year costs across all cancers was $14,534 in 1996 in U.S. dollars.[21] Furthermore, each increment in the intensity of follow-up usually generates large costs and diminishing returns. If only a small proportion of patients benefit, surveillance rarely looks attractive in cost-effectiveness analyses.[22]

Reflecting the uncertainty around most surveillance recommendations, ASCO only has surveillance guidelines for two cancer sites. The breast cancer guidelines (Table 2) are decidedly minimalist because of evidence that intensive surveillance does not improve outcomes. The colorectal guidelines (Table 3) have recently become a bit more intensive following publication of meta-analyses that suggest a small benefit for strategies that include imaging.[23] For other sites, surveillance practices are based largely on tradition coupled with patient demands, medical–legal concerns, and the constraints of third-party payers. It is important to realize these limitations, and before adopting a given surveillance strategy consider whether it is likely to detect recurrences earlier than they would otherwise become apparent, whether earlier intervention will improve patient outcomes, and whether these benefits are achieved in a cost-effective manner.

4.1.2. Long-Term and Late Effects of Treatment

Long-term effects are those that first occur during cancer treatment and persist after completion of primary therapy. An example would be scarring from surgery. Late effects, on the other hand, are toxicities that are not apparent during primary treatment but manifest clinically some time later, such as second cancers from radiation or chemotherapy.

Specific late effects vary greatly depending on the site of disease and treatment modalities involved. Many patients recover from resection of an early stage colon

Table 3. ASCO Colorectal Cancer Surveillance Guidelines[4]

- History and physical examination every 3–6 months for the first 3 years, every 6 months during years 4 and 5, and subsequently at the discretion of the physician
- Carcinoembryonic antigen every 3 months postoperatively for at least 3 years after diagnosis
- Annual computed tomography (CT) of the chest and abdomen for 3; pelvic CT scan for rectal cancer surveillance
- Colonoscopy at 3 years after operative treatment, and, if results are normal, every 5 years thereafter; flexible protosigmoidoscopy every 6 months for 5 years for rectal cancer patients who have not been treated with pelvic radiation

Chest x-rays, CBCs, and liver function tests are not recommended, and molecular or cellular markers should not influence the surveillance strategy based on available evidence.

Table 4. Common Long-Term and Late Effects of Cancer Treatment

Surgery	Radiation	Systemic therapy
• Cosmetic effects • Functional disability from removal of a limb or organ • Damage to an organ (bowel, bladder, sexual organs) • Pain • Scarring/adhesions • Incisional hernia • Lymphedema • Systemic effects (removal of endocrine organs, infection risk post-splenectomy)	• Second malignancies • Neurocognitive deficits • Xerophalmia, cataracts • Xerostomia, dental caries • Hypothyroidism • Pneumonitis, pulmonary fibrosis • Coronary artery, valvular, conduction, cardiomyopathic, and pericardial disease • Bowel stricture • Radiation proctitis • Bladder scarring • Infertility, impotence, premature menopause • Lymphedema • Bone fractures	• Second malignancies (myelodysplasia and leukemia) • "Chemo brain" • Cardiomyopathy • Renal toxicity • Premature menopause • Infertility • Osteoporosis • Neuropathy

cancer with little more than an abdominal scar, while those treated with mantle radiation for Hodgkin's disease face the prospect of subsequent cardiovascular morbidity and iatrogenic cancers.[24] The challenge when following cancer patients is to recognize potential problems related to their prior cancer, but still to monitor and work up problems judiciously. This may mean simply having a lower threshold for investigating dysphagia with endoscopy for esophageal stricture or malignancy following radiation, but not doing routine annual endoscopic surveillance for the possibility of such an unusual complication. Cancer survivors, like the rest of us, are aging and have other comorbid conditions. Consequently, it may be difficult to determine whether relatively vague complaints like fatigue need to be aggressively worked up as a possible harbinger of a cancer recurrence, or managed as it would be in a patient without a history of cancer.

Although not comprehensive, what follows is an overview of some of the more common long-term and late effects of cancer treatment categorized according to those resulting from surgery, radiation, and systemic treatments (chemotherapy, hormonal manipulation, etc.). Table 4 lists some selected common late effects.

4.2. Surgery

4.2.1. Cosmetic Effects

Most apparent but not always sufficiently addressed are the cosmetic effects of surgery. Patients may be embarrassed by their own distress from a seemingly minor problem with an otherwise good outcome and consequently may not bring forth their concerns. Nonetheless, visible scars from cancer surgery can result in some cases in social isolation. Other patients find the sight and smell of an ostomy to be repugnant and greatly overestimate how much it is apparent to others around them. It is incumbent on providers caring for these patients to explore these issues with them to ensure that they are as satisfied as possible with long-term cosmesis. If distress is identified, they should look for ways to optimize the cosmetic result, and where this is not possible, try to help the patient best cope with their situation.

4.2.2. Functional Problems

Surgical long-term and late effects usually result from damage to, or removal of, tissue and organs in the course of cancer surgery. Much of the time the effects are expected (e.g., menopausal symptoms following hysterectomy for ovarian cancer), while in other cases they are unintended (e.g., dumping syndrome after a partial gastrectomy). For example, surgery may leave the head and neck cancer patient without a voice or the ability to swallow, or may have resulted in the loss of a limb for a sarcoma patient. Physical, occupational, and speech therapists are among the multidisciplinary specialists that can greatly help cancer survivors with these disabilities optimize their function and activity.

4.2.3. Thoracic Surgery

Pain is another important yet common long-term effect of surgery. In most cases, the pain may be intermittent and less severe, such as discomfort from a "pulling" sensation caused by scarring after lumpectomy.[25] However, in the post-thoracotomy pain syndrome, the discomfort can be constant and disabling. It is felt to be possibly due to scar tissue involving the intercostal nerves that run along the ribs.[26] Pneumonectomy can leave patients with decreased pulmonary reserve resulting in dyspnea on exertion and increased propensity for pneumothoraces, pulmonary edema, or infection. Rarely, there can be compression of mediastinal structures due to mediastinal shift.[27] Post-thoracotomy pain can often require oral analgesics, and in refractory cases nerve blocks and epidural anesthetic pumps.

4.2.4. Abdominal Surgery

Any abdominal surgery, whether for cancer or not, can put patients at risk for intestinal obstruction from adhesions. The cause of intestinal obstruction can be difficult to determine as it could also be a sign of peritoneal recurrence of cancer rather than benign adhesions. Peritoneal carcinomatosis can be very difficult to demonstrate without surgical exploration, as it often is not apparent on imaging. As a result, patients with this complication are often extensively investigated with each episode, at great anxiety and expense. Surgical lysis of adhesions is usually a treatment of last resort as it risks simply creating more adhesions, but it is indicated in some patients with repeated severe episodes of bowel obstruction.

Incisional hernia is a common complication of abdominal surgery that is often quite troubling to patients. Some report discomfort, although for the majority it is a cosmetic concern. Not uncommonly the initial fear will be that it represents a recurrent tumor. While surgeons often counsel to leave uncomplicated hernias alone, the risks of surgery and other complications (e.g., more adhesions) may be acceptable to some patients.

One of the colon's main functions is to reabsorb water from the stool. Consequently, a minority of patients are left with frequent, loose stools after colectomy. These patients often have to limit work, travel, and social activities because of their need to constantly be near a bathroom. There is usually some improvement over the course of the first few years as the remainder of the colon increases its capacity to absorb water. This can be aided by fiber supplements and antidiarrheals, but some patients are still left relatively disabled by the altered bowel function. Sometimes elective colostomy is required.

4.2.5. Pelvic Surgery

Bladder and bowel dysfunction can greatly affect patients' quality of life. The mechanism of injury to these organs from surgery in the pelvis is obvious, however, operations to remove tumors involving the brain and spinal cord can also impact urinary and bowel control. Urinary continence can be affected by any procedure in the pelvis, but prostatectomy and hysterectomy are the most common culprits. Pelvic muscle exercises and medications such as oxybutanin or tolterodine can be helpful, but some patients need further surgical intervention such as the implantation of prosthetic urethral sphincters. Damage to the autonomic nerves, such as during a prostatectomy, can also cause erectile dysfunction which may require pharmacologic or surgical management.

4.2.6. The Extremities

Amputation is the most obvious long-term effect of surgery on the extremities, but many other cancer operations also require sampling of regional lymph nodes. Lymphedema is a not uncommon late effect of these procedures. While this may have no noticeable downstream effects, like in colorectal cancer, when it involves dissection of lymph nodes draining the extremities, as in axillary dissection for breast cancer or a groin dissection in melanoma, it risks leaving patients without sufficient lymphatic drainage from a limb. The resultant lymphedema may take several years to become clinically apparent as fluid accumulation in the tissues is initially restricted by counteracting hydrostatic pressure within those tissues. As the tissues stretch and expand, however, the lymphedema accelerates. Functional disability from stiffness, pain, limited range of motion, and predisposition to cellulitis (which can further damage lymphatics and exacerbate lymphedema), coupled with the cosmetic effects, can be devastating. As a result, sentinel lymph node sampling is increasingly being used for cancers in such sites as the breast and skin (melanoma) in hopes of decreasing this morbidity. Early recognition of the potential for lymphedema and detection of subclinical swelling can allow institution of measures to prevent its progression such as massage, compression garments, and avoidance of infection, blood pressure cuff use, and blood draws in the affected limb.

4.2.7. Systemic Effects

Although surgery is a local treatment, its effects can be systemic. For example, removal of endocrine and sexual glands in the course of cancer surgery can leave patients hypothyroid, diabetic, osteopenic, or menopausal. Removal of, or damage to, the sexual organs can render younger patients infertile, and so maneuvers such as sperm banking and embryo freezing must be anticipated and offered prior to surgery. Splenectomy may put patients at risk of overwhelming sepsis from encapsulated organs, making it important to recognize this situation and ensure that vaccinations have been optimized.

4.3. Radiation

Like surgery, radiotherapy is a local treatment. As a result, the long-term and late effects of radiation are mostly confined to the structures in and around the tumor that was radiated. An important difference, however, is that while radiation can destroy some organs and tissues as effectively as surgical removal, it may leave others only weakened, damaged, or inflamed. Often symptomatic management is the only option to deal with these sequelae.

4.3.1. Second Malignancies

Second cancers now account for over 15% of the incident cases of cancer.[28] Common environmental or genetic exposures often put patients at risk of second primaries in the same or different sites, such as lung cancer in head and neck cancer survivors that smoked. Cancer treatment itself may be the exposure, however. Radiation-induced tumors typically occur at the edge of a radiation field where normal tissue is damaged but not killed by radiation, and usually present 8–20 years after radiation. Perhaps the best described are risks of lung and breast cancer after mantle radiation for Hodgkin's disease. Skin in a radiation field has a greater risk of developing skin cancers.[29] Abdominal radiation is also associated with gastrointestinal malignancies. Rectal cancer is more common after radiation for prostate cancer. Myelodysplasia and acute leukemia can also develop after radiation. Treatment options for the secondary malignancy are not uncommonly limited because of the previous treatment, which is often in the same anatomic location. Physicians following these patients must be cognizant of these increased risks and consider interventions such as screening for breast cancer and tobacco cessation counseling.

4.3.2. Cranial Irradiation

Cranial irradiation can be the primary or adjuvant treatment for brain tumors, and may be carried out prophylactically, for example, in limited-stage small cell lung cancer and some hematological malignancies. While neurons do not have the rapid dividing characteristic usually targeted by radiation, radiation has effects on their glial supports and vasculature. Leukoencephalopathy typically occurs at doses above 55 Gy and appear 1–2 years following treatment.[30] As a result, slowed mentation and memory problems are well documented among these patients, and in some cases dementia, ataxia, and dysarthria also result. These effects can often best be managed with the use of accommodations such as slowing activity down, reducing multitasking, or compensatory strategies such as use of notes to aid memory.

The eyes and their surrounding structures can receive radiation in the course of brain irradiation or total body irradiation. This commonly results in dry eyes (xerophthalmia) which can lead in turn to corneal abrasions. Artificial tears can palliate this symptom. Patients whose eyes have been radiated are also at increased risk of developing cataracts. Radiation involving the ear can damage the acoustic structures, and this occurs more commonly than damage to the auditory nerve. Consequently, bone conducting hearing aids can yield effective amplification.

Radiation to the head and neck frequently destroys salivary glands. The resultant xerostomia can be very uncomfortable. It can also leave the teeth prone to bacterial overgrowth and decay as the saliva no longer effectively cleanses the mouth of normal oral bacteria. Consequently, attention to oral hygiene and prophylactic dental care is extremely important for head and neck cancer survivors.

4.3.3. Chest Radiation

Chest irradiation can damage any of the structures in the chest. For example, breast irradiation can in some cases interfere with lactation.[31] Acute radiation pneumonitis can progress to long-term focal pulmonary fibrosis and decreased lung capacity in a minority of patients. Its risk is related to both the total dose delivered and the volume of lung treated.[32] Dyspnea and cough are the most common symptoms, and imaging shows interstitial fibrosis which can be progressive. It can eventually lead to reduced diffusion capacity, lung volume, and compliance.[33]

Clinicians have long recognized that radiation can accelerate coronary artery disease. It is more recently being recognized, however, that it can lead to other cardiovascular sequelae, such as valvular disease, restrictive pericarditis, systolic and diastolic dysfunction, and conduction abnormalities.[34] Patients that had radiation for a left-sided breast cancer are at higher risk of cardiac mortality than those with right-sided breast cancer.[35,36] Radiation can also increase the risk of cardiomyopathy associated with anthracyclines (described below under systemic therapy). Patients who have had neck irradiation are at increased risk of stroke,[37] and abdominal radiation can lead to renovascular hypertension. Newer techniques designed to minimize these effects have decreased the risk for patients in recent years.[38] In addition to being aware of these problems, optimization of modifiable risk factors such as smoking and lipid levels should be encouraged.

4.3.4. Abdominal Radiation

Radiation fields that include elements of the gastrointestinal tract can cause scarring and strictures. These most commonly occur in the small bowel, but they can also occur in other areas like the esophagus. Strictures develop as a late effect and present with obstructive symptoms. Therefore, like adhesions, they can be confused clinically with possible cancer recurrence. It is important to recognize that radiation to the spleen can render patients functionally asplenic, with all the same implications for infectious risk as with surgical removal.

4.3.5. Pelvic Radiation

Pelvic radiation can cause long-term radiation proctitis in a minority of patients. Analogous to the symptoms of a bladder infection, the inflamed rectum seeks to immediately discharge any small amount of stool that enters it. As a result, these patients can have severe fecal urgency and frequency, with each movement consisting of a disappointingly small amount of stool. Antispasmodics like Levsin or Anusol suppositories can help, and symptoms usually improve over the course of a couple of years. However, some patients with persistent debilitating symptoms eventually elect colostomy.

The bladder can be scarred from radiation, resulting in persistent irritative symptoms or decreased capacity. These complications can actually sometimes worsen with time.[39] Medications for urge incontinence like oxybutynin or tolterodine may be helpful. Brachytherapy, increasingly used in early stage prostate cancer, is less likely to cause bladder problems than is external beam radiation. Radiotherapy can also leave the vagina dry and scarred, requiring vaginal lubricants and dilatation procedures to ameliorate.

Pelvic radiation can damage fertility. Primary or adjuvant radiation for cancers of the pelvis will render most women infertile, even if ovaripexy (surgically moving the ovaries out of the radiation field) is performed, likely due to the scatter of radiation outside of the intended field.[40] Unfortunately, there is often insufficient time to stimulate and harvest ova prior to therapy. Radiation doses to the ovaries as low as 20 Gy induces premature menopause in women under 40 years, and as little as 6 Gy will induce ovarian failure in women between 40 and 50 years.[41] Male testicles are even more sensitive to radiation. Spermatogenesis will be affected with doses as low as 0.2 Gy, and may be permanent above 1.2 Gy.[42] Gonadal shielding can be somewhat effective but cannot be relied upon to preserve fertility.

Pelvic radiation can damage the autonomic nerves responsible for erection. As a result, erectile dysfunction is common after radiation for prostate, rectal, and anal cancers.[43] Improvement often occurs over the first year after treatment but then stabilizes. As important as evaluating the degree of erectile dysfunction is evaluating how much this bothers the patient; some patients are untroubled by complete loss of function while others are extremely distressed by even relatively subtle changes in sexual function such as retrograde ejaculation. Erectile dysfunction can be managed with oral agents like sildenafil, tadalafil, and vardenafil, but sometimes requires external suction devices, penile injection therapy, or implantation of penile prostheses. Referral to a urologist specializing in male sexual health can be very helpful.

4.3.6. The Extremities and Bone

Radiation can damage lymphatics and cause lymphedema independently of surgery. When combined with surgical lymph node dissection, however, the risk of lymphedema is compounded.

Radiation weakens bone. For example, painful sacral fractures are a late effect of pelvic radiation that can be concerning for local recurrence or osseous spread of a malignancy like rectal cancer. A history of radiation is associated with increased risk of spinal compression fractures within the field. Recently an increased risk of hip fracture has also been recognized following pelvic radiation.[44] Providers must recognize that in these patients osteopenia and osteoporosis may be focal, and if present, consider interventions such as bisphosphonates and recommendations for weight-bearing and muscle-strengthening exercise.

4.3.7. Systemic Effects

The hormonal effects of radiation are similar to those associated with surgery, being a localized treatment that can damage organs and glands with systemic implications. Radiation of the thyroid, classically in mantle radiation for Hodgkin's disease and also for other cancers such as non-Hodgkin's lymphoma or head and neck cancer, commonly induces hypothyroidism.[45] It is dose-dependent, increasing with doses above 25 Gy, and usually occurs within 2–3 years.[46] Much less frequently, cranial irradiation to doses above 50 Gy can affect the hypothalamus and pituitary leading to central hypothyroidism.[46,47] The National Comprehensive Cancer Network (NCCN) guidelines (www.nccn.org) recommend at least annual TSH monitoring for hypothyroidism in patients who have undergone neck irradiation. Thyroid cancer can also develop in a radiated thyroid, and so there should be a low threshold to biopsy thyroid nodules in such patients.[48]

4.4. Systemic Therapy

Whereas the long-term and late effects of surgery and radiation are determined by the site of the primary tumor, the effects of systemic therapy are related to the drugs involved.

4.4.1. Second Malignancies

Like radiation, chemotherapy is associated with second malignancies. The most common iatrogenic cancers attributable to systemic treatment are myelodysplasia and acute leukemia. These are usually associated with drugs that have alkylation as at least one of their mechanisms of action. Classic alkylators like cyclophosphamide contain an electorphilic alkyl group with an affinity for the N7 position on guanine. As a result, it intercolates itself between DNA strands causing mispairing of neucleotides and single and double strand breaks. Other drugs, such as the platinums, anthracyclines, and epipodophyllotoxins, have a nonclassical alkylating mechanism that achieves similar effects on DNA through electrostatic means. This DNA damage, if it activates an oncogene or inactivates a tumor suppressor, can lead to transformation of cells and neoplasia. There are other examples of secondary cancers resulting from primary systemic cancer therapy. For example, tamoxifen can cause uterine cancer through hormonal stimulation of the endometrium, and the chronic cystitis resulting from cyclophosphamide and ifosfamide may lead to bladder cancer.

4.4.2. Cognitive Effects

"Chemo-brain" is being increasingly recognized as a constellation of mild cognitive problems associated with prior exposure to multiagent chemotherapy. It has also been reported in men on testosterone suppression. The most common symptoms include problems with mentation, concentration, and memory. While several studies have shown this to be an actual phenomenon,[49] the specific mechanisms are unknown. Moreover, it is not clear that chemotherapy itself causes these symptoms as detectable pretreatment impairment of cognition has been demonstrated in cancer patients.[50] As well, those with greater psychological distress are more likely to develop cognitive dysfunction. Management includes ruling out other treatable organic causes, including depression. Nonspecific treatments such as the stimulant methylphenidate have not clearly been shown to ameliorate this syndrome.

4.4.3. Cardiovascular Complications

Cardiac late effects are most closely associated with the anthracycline class of chemotherapeutic agents (doxorubicin, mitoxantrone, epirubicin). One of the mechanisms by which these drugs work is the creation of free radicals which damage the DNA of replicating cancer cells. However, free radicals also damage normal tissue. Cardiac muscle is particularly vulnerable because it lacks sufficient glutathione, which neutralizes free radicals. As a result, cardiac muscle accumulates progressive damage with increasing exposure to anthracycline drugs resulting in cardiomyopathy and congestive heart failure. This may also lead to arrhythmias. Consequently, the anthracycline class of chemotherapeutic agents each has limits above which exposure is not considered safe: for example, 450 mg/m^2 for doxorubicin and 900 mg/m^2 for epirubicin. Several drugs commonly combined with anthracyclines in breast cancer, such as cyclophosphamide, paclitaxel, and herceptin also have cardiac toxicity, thereby compounding the possibility of adverse cardiac effects. These latter drugs mostly contribute to acute toxicity, however. Cisplatin has also recently been recognized as having vascular toxicity in addition to contributing to dyslipidemia.[51]

Patient characteristics associated with cardiac long-term and late effects are older age and preexisting cardiac disease. Premature menopause from cancer therapy can adversely affect lipid profiles and accelerate atherosclerosis, as can the effects of some hormonal treatments. Cancer patients can also be at increase risk of venous thromboses because of hormonal effects on coagulability and vascular irritation from chemotherapy and implanted devices. Cardiovascular adverse effects can remain subclinical for many years before causing overt symptoms, often making the link with prior cancer therapy nonobvious.

4.4.4. Sex Hormones and Reproduction

Chemotherapy, particularly alkylating agents like cyclophosphamide, can induce infertility and, in women, premature menopause, with its attendant problems of hot flashes, mood swings, vaginal dryness, and urinary incontinence. Cyclophosphamide is commonly used in breast cancer, but management of the menopausal symptoms is complicated by the fact that hormone replacement therapy is considered contraindicated in patients with a history of breast cancer. Consequently, other treatments must be used for hot flashes, such as antidepressants.[52] This example illustrates the importance of both recognizing the symptoms related to ovarian failure in a cancer patient in which it would be otherwise unexpected, and having knowledge of the oncologic considerations of the therapies being chosen.

In general, the younger a patient is, the more likely they are to have their fertility preserved after chemotherapy.[53] However, breast cancer patients are usually advised to delay childbearing for at least 2 years after diagnosis because of their relatively high risk of early relapse. Moreover, the effects of adjuvant hormonal therapies on pregnancy are unclear and so patients are advised not to conceive while taking them. These delays can by themselves impair chances of conception. Although there is controversy, there is not clear evidence that pregnancy increases the risk of relapse, or that there is increased risk of birth defects in cancer survivors.[54] Technologies for assisted reproduction for women, like cryopreserving ovaries, are not yet as successful as sperm banking is for men.

Alkylators also affect male fertility, but fertility usually recovers within 2–3 years. Studies have shown that more than half of testicular cancer patients have impaired spermatogenesis even before they develop their cancer. As a result, it has been difficult to evaluate the contribution of drugs like cisplatin to fertility problems in males.[42,55]

Among breast cancer survivors, sexual dysfunction appears to be more closely related to receipt of chemotherapy[56,57] than the body image concerns resultant from mastectomy[58] or tamoxifen effects,[59] although all may play a role.[60] Many of these symptoms improve with prolonged (i.e., >5 years) follow-up.[61]

4.4.5. Bone Health

Bone health can be impaired in many ways. Premature menopause induced in women by any of the mechanisms related to surgery, radiation, or systemic therapy predisposes to osteopenia and osteoporosis. Steroids, whether given as part of primary treatment or as adjunctive therapy with analgesics or antinauseants also weaken bone. They are also associated with avascular necrosis. Lastly, hormonal treatments for breast and prostate cancer accelerate bone loss, osteoporosis, and fractures.[62] The endocrinology is complex, however. Tamoxifen can preserve bone mineral density in post-menopausal women but is associated with bone loss in younger women.[63] Aromatase inhibitors adversely affect bone density in all ages.[64] Consequently, ASCO recommends regular monitoring of bone mineral density with dual energy x-ray absorptiometry, dietary intake of calcium and vitamin D, weight-bearing exercise, and smoking cessation.[65] Bisphosphonates can be useful for the treatment of osteoporosis.

4.4.6. *Miscellaneous Effects of Systemic Treatment*

A series of other long-term and late effects are associated with specific systemic cancer drugs. For example, bleomycin causes pulmonary fibrosis at doses above 450 mg/m^2, especially in the elderly and those on supplemental oxygen,[66] and the acrolein metabolite of cyclophosphamide and ifosfamide causes a hemorrhagic cystitis that in a small proportion of unfortunate patients can become chronic after a severe acute episode. Cisplatin can affect renal function, which can be either acute or of delayed-onset. Vinca alkyloids like vincristine cause sensory neuropathy, as do platinum drugs (cisplatin, oxaliplatin) and taxanes (paclitaxel, docetaxel). Many of these can reverse to some extent but take many months or even years to do so. Cisplatin's ototoxicity is often permanent.[67]

4.5. Psychosocial Concerns

The majority of the evidence suggests that cancer survivors have good emotional functioning after cancer,[68] although rates of some diagnoses, such as depression, are higher among cancer survivors than in the general population.[69,70] Fear of recurrence and death understandably dominate adjustment disorders, and may reach the extent where they interfere with vocational and personal pursuits.[71]

Cancer survivors with preexisting anxiety or affective disorders appear to be at greatest risk for ongoing distress.[25] Changes to body image from cancer therapy, such as that resulting from mastectomy or colostomy, can be a source of problems with psychological adjustment.[72] Distress appears to dissipate with time, however. There are a small proportion of patients who experience ongoing effects characteristic of posttraumatic stress disorder.[73] Having a spouse or partner decreases the risk of psychological sequelae,[74] although these caregivers may also themselves be adversely affected.[75] Social networks[76] and support groups[77] have been found to improve mental health in breast and prostate cancer survivors.

Cancer appears to cause a greater detriment to the quality of life of younger patients than the elderly,[78,79] likely due to the greater disconnect between their expectations for health, physical functioning, and roles at that stage of life than when older. A small proportion of cancer survivors report persistent fatigue at levels above population norms. Depression and chronic pain are commonly associated with these cases.[80] Recurrence of cancer and late effects such as hypothyroidism must be ruled out. Exercise may help. Tools like the "Distress Thermometer" in NCCN guidelines, are available to assist providers in screening for symptoms of distress.

Some positive psychological effects of having been a cancer survivor have also been observed.[81,82] Sense of well-being has been reported to be better among cancer survivors than respondents without a history of cancer[56] and marital relationships may be strengthened.[70] These findings speak to the resilience of cancer survivors. Survivors can find themselves with a greater appreciation for life and a better ability to prioritize things, resulting in an overall positive impact on their lives.

4.5.1. Non-Cancer Health Care and Health Maintenance

The IOM report suggested in its title that many cancer survivors are "lost in transition" and that the quality of care suffers when patients and providers do not know what is expected after primary treatment ends. While much of the focus of research and guidelines has been on cancer surveillance, non-cancer health care is equally as, and in many cases more important than surveillance. Most patients diagnosed with cancer today are expected to survive it.[28] Studies have shown that potentially preventable conditions like heart disease and diabetes are actually the greatest threat to life for many of these patients.[83,84] As a result, despite the fact that a diagnosis of cancer tends to subjugate all other concerns for a while, preventive care and the management of other medical conditions may actually be more important in the long run.

The end of primary treatment for cancer has been called a "teachable moment."[85] This recognizes that with significant events in a patient's life, there is the opportunity to have a greater impact on health behaviors with programs that have been shown to help change risk behaviors than at other times. As a result, the survivorship care plan should include specific recommendations on lifestyle issues such as diet, exercise, smoking, and immunizations.

While studies have shown cancer survivors usually have more medical contacts than people without a history of cancer,[86] there is also evidence that they may not always receive the same quality of care for other medical problems such as diabetes or chronic lung disease.[87] A blinding focus on the prior malignancy or nihilism about the prognosis may leave cancer patients' other medical issues relatively ignored. The quality of routine care for cancer survivors has been shown to be related to their level of engagement in the health care system.[86,87] Patients followed exclusively by primary care physicians are less likely to undergo recommended surveillance for their cancer, while those who use oncologists as their primary care physicians may be less likely to receive recommended non-cancer care. Patients followed by both types of physicians consistently receive the highest quality care. One explanation for these observations is that there may be lack of clarity around the relative roles primary care and specialist physicians will play in a survivor's care. Alternatively, it is possible that there is a disconnection between the expectations of care among survivors and their various health care providers. Patients and primary care physicians may assume that cancer specialists are delivering care that they are not (e.g., screening for other cancers, checking lipid levels along with the tumor marker). Some patients may be looking to their specialist physician for primary care but the specialist may not be aware of it. In fact, a large survey of oncologists found that they generally do not want to take on that role.[88] Similarly, PCPs may assume either that there is still an oncologist involved when there may not be, or that that oncologist will assume responsibility for all cancer screening, not just surveillance of the original cancer.

The transition off of primary cancer treatment is also a second opportunity to consider whether genetic assessment might be necessary. During an initial consultation, when taking the family history, a potential genetic predisposition may be detected. However, the patient may not pursue referral to a genetic counselor at that time because they are so overwhelmed by the new diagnosis of cancer and dealing with the treatment they will have to embark upon. The completion of treatment is another opportunity to review this issue and consider making a referral. The genetics of breast, ovarian, and colorectal cancers are best understood, but increasingly associations with other cancers such as pancreatic cancer and melanoma are being recognized, although screening recommendations are not well developed. Patients may be offered participation in clinical research looking to better define surveillance strategies for high-risk patients (e.g., EUS screening for patients with heritable risk of pancreas cancer). Documentation of a genetic predisposition to cancer could affect not only recommendations for family members, but surveillance recommendations for the patient. For example, interval cancers are more common among patients with Hereditary Non-Polyposis Colorectal Cancer and so surveillance colonoscopies should be more frequent.

4.5.2. Employment, Insurance, and Economic Issues

Features that are recommended by the IOM to be part of the survivorship care plan that likely go beyond what cancer physicians view as current usual practice include information on the possible effects of cancer on marital/partner relationships, work, parenting, and the potential future need for psychosocial support. It also counsels that providers should furnish information on the potential insurance, employment, and financial consequences of cancer. For example, despite the Americans with Disabilities Act, some cancer survivors suffer discrimination in job loss, hiring, extension of benefits, or the ability to acquire affordable health insurance. One of the anticipated benefits of thinking about these nonmedical issues is that it might prompt, as necessary, referral to counseling, legal aid, and financial assistance. As these are often not areas of expertise for oncology providers, much of this may be initiated by giving patients a directory of cancer-related resources (e.g., online or telephone listings) and/or information in the form of general information brochures. Raising these issues with patients will at least let them know that help is available should they need it.

4.5.3. Barriers to Creating a Formal Survivorship Care Plan

The IOM and ASCO both endorse the idea that treatment summaries and survivorship care plans for systemic cancer treatment become part of standard practice and included in the medical record. Such documentation can greatly facilitate communication with other physicians about the treatments patients have received and what the known toxicities have been, while also providing information as to the late effects other providers should be on the lookout for. It would also assist efforts to monitor care patterns and evaluate the quality of care delivered. Barriers to achieving this include: reaching consensus about what information these summaries should contain; how they can be standardized, ideally in electronically searchable formats; how to create incentives, whether financial or otherwise, for busy oncologists to take the time to create them carefully; how their creation can be facilitated and simplified with information technology support; and changing the oncology culture so that treatment summaries become an expected practice. Clearly, the summary described in Table 1 would be a labor-intensive undertaking. On a larger scale, there are already manpower concerns in the oncology workforce brought about by the aging population, improved cancer therapeutics, and previous policy decisions limiting the training of specialist physicians. Spending more time on survivorship means there will be fewer available man-hours to care for patients with active cancer.

Creating a survivorship care plan is currently time consuming and difficult. Providers could attempt to create a document as they go along during the course of care, but realistically, busy oncologists are usually stretched to their limit dealing with the acute toxicities of treatment and are unable to also work consistently on posttreatment care planning. Standardization with templates could decrease the work required such that much of the data could be assembled by nonphysician staff such as nurses or nurse practitioners. Even with standardization and automation, however, creation of a survivorship care plan still requires time and resources, and so the concept of a formal discharge consultation has been proposed. This could be either with the patient's oncologist or other health provider, or in a dedicated survivorship clinic with comprehensive access to medical records. Currently there is no mechanism of compensation for such consultations, however. A change in reimbursement policy is needed to recognize the importance of posttreatment planning. With over 60% of cancer survivors being aged 65 and older, the Medicare program can not only facilitate this process, but could ensure it through incentives and regulations for payment.

4.5.4. Models of Care Delivery Systems

Clarity around who will be delivering various aspects of care to cancer survivors is often missing. One study found that a third of cancer survivors were not sure which physician was in charge of their cancer follow-up.[89] Some patients are aware of this and able to take responsibility for obtaining at least some of their necessary care. Others can be empowered if made aware of what the plan should be. There will always be a proportion of patients, however, who lack the knowledge or personality to advocate for themselves. As a result, one of the most valuable features of holding cancer providers responsible for a survivorship care plan may actually be defining explicitly which providers will take responsibility for different aspects of a patients' care.

There is no single organizational model that must be adopted to deliver high-quality care to survivors. Although the National Coalition for Cancer Survivorship articulated the proposal that "long-term survivors should have access to specialized follow-up clinics that focus on health promotion, disease prevention, rehabilitation, and identification of physiologic and psychological problems," in reality, whether follow-up is provided by oncologists, PCPs, or specialized survivor clinics is unimportant. The IOM's Committee on Health Care Quality in America affirmed that "care based on continuous healing relationships should be maintained. In other words, patients shouldn't be removed from the care of their treating PCPs and oncologists in order to receive specialized survivor care. Rather, survivorship care should be 'value-added'." Instead of focusing on exactly who is providing this care, it is most important that survivors have identifiable providers who communicate with each other and are able to recognize and address possible issues as they come up.

4.5.4.a. Shared Care. Cancer survivors make more office visits for cancer care with PCPs than with oncologists.[90] While this may often be due to insurer mandates or specialist availability, it is important to optimize the opportunity this presents. Oncologists often lack the time to adequately provide all care to all cancer patients and survivors. Moreover, there is not sufficient manpower to sustain an entirely specialist-based model of survivor care given the nation's growing population of cancer survivors. PCPs are better positioned and qualified to ensure that the full spectrum health needs of cancer survivors are addressed, including not only issues surrounding their cancer but also health maintenance (prevention), the management of concurrent comorbid disease (e.g., heart disease, diabetes), mental health, and acute care. As a result, the IOM endorses the concept of “shared care” in which PCPs collaborate with cancer specialists to ensure the delivery of high-quality survivorship care.

The role of oncologists in a shared-care model is to provide or guide periodic surveillance and to be available to evaluate patients when concerns arise. They must also keep the primary care physician informed of the treatment plan both initially, when the patient completes primary therapy, and as their disease evolves. During, as well as after the period when the patient is being seen by the cancer specialist, ongoing primary care is important to maintain treatment of other coexistent conditions and to follow up on implementation of the care plan initiated by the cancer specialist.

There are great challenges for the PCP who wishes to take care of survivors. Cancer care is often fragmented among many different specialists, and there has traditionally not been adequate communication back to PCPs of such basic information as the specific diagnosis, stage, and treatment received. Moreover, the lack of clear practice guidelines for survivors creates uncertainty. Shared care works best when it is supported by a health care delivery system with infrastructure that facilitates access to medical records between providers and seamless “handoffs” of care. A properly executed survivorship care plan as proposed by the IOM could help mitigate many of these problems.

4.5.4.b. Specialized Survivorship Clinics. Another model for delivering survivorship care is in dedicated clinics in which expertise is concentrated and the efficiencies of specialized practice can be realized. Few of these currently exist, however. Some are designed primarily to take over the mechanics of surveillance. Others focus on providing primary care, especially to disadvantaged populations. Still others take on a consultative role looking for signs and symptoms of long-term and late effects and then making appropriate referrals. They are often run by specialized nurse practitioners. Under any model, an advantage of a dedicated clinic is that it provides the patient an opportunity away from what might otherwise be a quick “good news” visit with the oncologist, to focus on aspects of their survivorship other than just whether there has been a recurrence and bring up issues that might otherwise seem minor in comparison, like sexual dysfunction, that may be significantly affecting their lives. The separate, dedicated survivorship visit also provides an opportunity for another provider to do a comprehensive review of the patient’s care, sometimes spotting an opportunity for a genetics referral, providing lifestyle counseling, noticing an abnormal screen that was not followed up, or some other health maintenance intervention that may have been overlooked. It also provides a forum for patients to ask informational questions about their disease or its treatment that they might not want to “bother” their oncologist with, or seek advice on nutrition, exercise, and complementary and alternative medicines that they may not feel comfortable speaking about with their cancer physicians. Furthermore, specialized clinics can be a mechanism to assist the oncologist in the creation of a treatment summary and survivorship care plan. It can also be an efficient avenue for recruiting survivors into research protocols.

5.0. RESEARCH NEEDS

The IOM stated that survivorship care plans “have strong face validity and can reasonably be assumed to improve care unless and until evidence accumulates to the

Table 5. Examples of Key Quality of Care Research Questions for Cancer Survivors

- Basic science studies to elucidate the mechanisms of late effects
- Observational studies to assess the incidence and predictors of late effects
- Clinical trials of interventions (medical, psychological, risk behaviors) to prevent or reduce the severity of physical or psychological late effects
- Evaluation of the effectiveness of different surveillance strategies on survival, quality of life, and cost
- Examining whether disparities exist in the quality of care provided to survivors of different ages, racial and ethnic groups, sexes, socioeconomic status, and diagnoses
- Exploring the effect of cancer on a survivor's family and caregivers
- Development and validation of instruments able to capture important outcomes specific to the survivor population
- Observational studies to determine survivors' knowledge of the content of the survivorship care plan (i.e., their diagnosis, previous treatment, plan for surveillance and monitoring, resources available and who to turn to for different problems, etc.)
- Assessing variation in practice patterns and outcomes by geography, patient and provider characteristics, organizational and insurance structure, etc., and whether disparities in the quality of follow-up care exist
- Determining the current and optimal levels of involvement of different specialists and PCPs in cancer follow-up and ongoing care
- Evaluating ways to optimize portability of medical records (smart cards, web-based data) for the increasingly mobile survivor population
- Determining the cost-effectiveness of different survivorship care plan strategies
- Creating and validating quality measures related to survivorship care plans

contrary" and calls for research to assess both the effectiveness and cost-effectiveness of survivorship care plans, as well as their acceptance by both cancer survivors and health care providers. Table 5 provides examples of quality of care research questions important for the management of the growing survivor population. Survivorship research presents several methodological challenges, however, especially when looking at interventions such as surveillance that may affect survival outcomes. Randomized trials are required because nonrandomized studies are susceptible to lead-time and length-time biases. Randomized trials are logistically difficult and expensive to carry out, however, because they have to be very large to detect usually very small differences. Furthermore, what is tested is generally a complex strategy, and so the chosen components, frequency, and duration of surveillance are open to question. Moreover, overall survival outcomes may be confounded by ever improving treatment for relapsed disease. Recent changes in privacy laws can be a barrier to population-based survivorship research by preventing researchers from identifying and contacting former patients. Despite these problems, investment in survivorship research must continue. The evolution of cancer therapies means that late effects we see now may be replaced by new unanticipated concerns for our current patients in years to come. Consequently, information is needed ranging from basic science studies to delineate mechanisms of late effects, to health services research to ensure that outcomes are optimized with good value for the money.

6.0. CONCLUSION

The ever increasing population of cancer survivors is just now being recognized as a distinct population with a lot of common health and social issues. Still, the care they are in need of must be individually tailored. As a result, a focus on clarity about the roles of different providers in the management of survivors and an explicit plan going forward are the most important aspects of high quality survivorship care. Whether or not a formal consultation and survivorship document becomes standard practice, the principles articulated in the IOM recommendations will ensure that the transition along the cancer trajectory from patient to survivor can be as smooth as possible.

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Chapter 4

Quality of Life in Long-Term Cancer Survivors

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1.0. INTRODUCTION

Due to improved diagnosis and treatment, 59% of persons diagnosed with cancer today will survive their disease for at least 5 years from the time of diagnosis.[1] Overall, it is currently estimated that over 9.6 million persons living in the United States are cancer survivors.[1] While there is a growing body of literature on the physical, psychological, and social difficulties of survivors[2]; fewer studies focus on persons who are long-term, that is, 5-year survivors.[3–6]

According to SEER (surveillance, epidemiology, and end results) data,[7] the percentage of persons who have survived more than 5 years after being diagnosed with cancer has increased over the past two decades. For men, large gains in cancer survival rates (more than 10%) were seen in cancers of the prostate, colon, and kidney, and non-Hodgkin lymphoma, melanoma, and leukemia. Modest gains (5–10%) were found for cancers of the bladder, stomach, liver, brain, and esophagus.

For women, large gains in cancer survival rates were seen for colon, kidney, and breast cancers and non-Hodgkin lymphoma. Modest gains were found for bladder, oral cavity, stomach, brain, esophageal, and ovarian cancers and melanoma and leukemia.

Limited survival improvement was noted in adults diagnosed with cancers of the lung, pancreas, and liver, cancer that are often characterized by late stage at diagnosis and relatively limited survival rates even when diagnosed at a localized stage. There was also little or no gain in several cancers with generally high survival rates, including larynx, thyroid, and uterine cancers. Survival statistics in the United States still favor the more affluent and Euro-American population; the survival rate of non-Euro-Americans has been estimated to be 5–15% lower.[8,9]

The focus of this chapter is on the quality of life (QOL) of men and women whose cancer diagnosis occurred at least 5 years in the past. Seven years ago, a seminal review of long-term QOL in long-term cancer survivors was completed.[3] Therefore, we will consider the research from 1998 and beyond in this chapter. While our research has focused mainly on breast cancer, we review recent research on breast cancer, Hodgkin's disease, and prostate cancer.

After defining QOL and describing the framework to be used in this review, four different aspects of the QOL will be considered. First, much of the literature that is accumulating on this topic focuses on individuals' responses to the cancer experience. After a brief discussion of the early effects of the diagnosis and initial treatment on QOL, we review research documenting the late effects of the diagnosis and treatment on survivors. This continues to be an important consideration, especially as more reviews are tackling multiple cancer sites. Second, for purposes of comparison, we juxtapose our research on breast cancer with our research on Hodgkin's disease survivors' QOL. Third, given that most cancer survivors live with family members and interact with both friends and relatives, we review the literature on family members' reactions to long-term survivorship and the impact of family history of cancer (i.e., breast and prostate cancer) on QOL. Finally, our nation is rapidly becoming multiethnic. Cancer survivors also are multiethnic and come from different cultures. So, to the extent possible, we also focus on racial and ethnic difference in the cancer experience. We close the chapter with a discussion of directions for future research.

2.0. METHODS

We searched the PsycINFO and MEDLINE databases for relevant articles. Included in the review are articles published in 1998 or later, following the comprehensive review by Gotay and Muraoka,[3] and focused on more than one dimension of QOL. Thus, a study focusing only on comorbidity would not be included. The sample had to be, at least, 5 years post-diagnosis. In studies whose sample ranged in the number of years following diagnosis, a measure of time post-diagnosis/treatment needed to be included so that we could determine whether longer term survivors fared better (or worse) on the dimensions of QOL. And the sample had to be sufficiently large to have statistical power for drawing conclusions from the analysis. Studies that focused solely on qualitative analysis are not included. While cross-sectional studies are the most represented group in the review, those with non-cancer or another cancer site as a comparison, and some longitudinal studies also are included.

Also included in the chapter are findings from studies conducted by the lead authors and her colleagues on survivors of breast and prostate cancer and Hodgkin's disease.

3.0. QOL FRAMEWORK

Improvement in QOL among cancer survivors has been a goal of cancer management for years. While mortality rate has been the primary focus, once survival is more likely the QOL of those with cancer becomes more of a concern. The notion of QOL directs attention to the "complete social and psychological being: the individual's performance of social roles, mental acuity, emotional state, sense of well-being and relationships with others."[10] Quality of life has been defined as the difference, or the gap, at a particular period of time between the hopes and expectations of the person and one's present life experiences.[11,12] In other words, the concept encompasses not only the person's objective state, but also the extent to which that objective state and the person's expectations and hopes are congruent. Without the person's assessment of the meaning of his current situation, there is no way of calibrating the experience. Two people may have exactly the same objective state of health, but their QOL may be perceived as being quite different.

Quality of life is dynamic and changes over time. It is modified by age and experience. Older people adjust their perception about their QOL, whereas younger people may hold higher expectations concerning their physical and functional status. The finding that ratings of QOL tend to be better in older compared to younger people supports this observation.[13,14]

The concept of QOL is not unidimensional, but instead covers a number of life domains. For each domain, QOL may be perceived differently and be differentially weighted. Changes in one domain can influence perceptions in other domains. Thus, disruption in the physical domain is likely to affect the individual's psychological or social well-being. While many [12–14] different domains have been described[10] most generally QOL is defined as including physical, psychological, social, and spiritual domains.[15–17] It is generally considered that QOL is best defined and measured from the individual's perspective.

In measuring the perceived QOL of cancer survivors, Ferrell and colleagues present a model that includes four domains—physical, social, psychological, and spiritual.[15,18] We use Ferrell and colleagues model as the framework for discussion in this chapter. The four QOL domains are defined as follows.

- *Physical well-being* is the control or relief of symptoms and the maintenance of function and independence.
- *Psychological well-being* is the attempt to maintain a sense of control in the face of life-threatening illness characterized by emotional distress, altered life priorities, and fear of the unknown as well as positive life changes.
- *Social well-being* is the effort to deal with the impact of cancer on individuals, their roles, and relationships.
- *Spiritual well-being* is the ability to maintain hope and derive meaning from the cancer experience which is characterized by uncertainty.

While a separate chapter will be devoted to the measurement of QOL and some newer approaches in measurement, we provide a brief overview of measurement to place our research in perspective. Early studies of QOL focused on psychological measures of outcomes that were developed for individuals with acute and persistent mental illness.[19] Since then, more global measures of QOL have been developed.[16,17,20–22] The need to measure not only the problems resulting from a cancer diagnosis but also the positive benefits of surviving a life-threatening diagnosis and treatment has also been put forward.[23]

The recent and cancer-specific measures of QOL have been designed for adult populations.[16,17,20] Quality of life measures were originally designed for clinical trials in the United States (e.g., Cella and Tulsky designed the FACT while Aaronson and his colleagues designed the EROTC for clinical trials in the European Community). While cancer survivors share a common experience, irrespective of their background or diagnosis, there are also aspects of the experience that are uniquely related to their specific cancer and its treatment. Most clinical researchers designed their measures by using a general set of indicators plus a set that could be tailored to the specific cancer site (e.g., breast, prostate, colorectal), yet sufficiently parsimonious for use in clinical trials. However, many of the studies reviewed in this chapter used the Medical Outcomes Study, Short Form (SF)-36 or SF-12,[24,25] a more general measure of health-related QOL. Typically, they have added items relevant to the specific cancer(s) that were being studied. Quality of life instruments used in each of the articles reviewed are listed in Tables 1–3.

4.0. EARLY EFFECTS OF THE DIAGNOSIS AND INITIAL TREATMENT ON QOL

Although not included in our review, most studies of cancer survivorship and QOL focus on the immediate post-diagnostic and posttreatment periods. Some of the earliest systematic work on breast cancer was conducted by Morris and her colleagues[26] and by Maguire and his colleagues,[27] on Hodgkin's disease by Fobair *et al.*,[28] and on prostate cancer by Litwin *et al.*[29] Early work on emotions is exemplified by the Psychological Aspects of Breast Cancer Study (PABC).[19] Almost three decades ago, longitudinal data collected at 3 month intervals indicate that, over time, the dysphoria associated with diagnosis of early breast cancer (Stage I and Stage II) lessens and that emotions stabilize. By the end of 1 year, the psychological profile of women with breast cancer was found to not be significantly different from that of women who did not have cancer.[19] A more recent study reaffirms these early findings and did not find further improvements when the cohort was compared at either 2 or 3 years later.[30] The study by Morris and colleagues,[28] indicated that emotional problems prior to the breast cancer diagnosis were exacerbated following diagnosis and treatment. To separate the effects of preexisting emotional difficulties from those related to the diagnosis and treatment of breast cancer, both the PABC and the Ganz studies excluded women who had such problems.[19,30]

Also with regard to breast cancer, most studies indicate that the major difference between breast sparing surgery and a mastectomy are found in body image with poorer body image being associated with mastectomy.[31] In our study of breast cancer survivors we also found that among those who had a mastectomy, women who chose reconstruction compared to those who hadn't yet decided had the poorest body image.[32]

There is also consensus regarding a third set of findings from this literature on early effects of diagnosis and treatment with regard to the physical realm. These include menstrual changes and menopause, infertility, sleep problems, lymphedema, pain, problems with physical and recreational activities, and weight gain and reduced energy.[15,18,30,32–40] Ganz found nearly identical rates of arm problems 2 and 3 years posttreatment related to the initial surgical procedure (numbness, tightness and pulling in the arm, and intermittent mild pain).[30] Other early effects are energy reduction, decreases in physical functioning, and symptom distress as found in our early study of Hodgkin's disease.[28] Sexual, urinary, and bowel function changes are specific to prostate cancer.[29]

5.0. LATE EFFECTS OF THE DIAGNOSIS AND TREATMENT ON QOL: LITERATURE REVIEW 1998–2005

In this section, we review literature published between 1998 and 2005 on the long-term QOL among breast cancer, Hodgkin's disease, and prostate cancer survivors.

Literature is summarized according to Ferrell and colleagues' four domains of QOL.[15,18]

5.1. QOL in Long-Term Survivors of Breast Cancer

Study characteristics: In total, 16 studies met our search criteria for breast cancer, all published after 1998. The studies are described in Table 1 and include our study,[32] which will be discussed in greater detail following the general review. Quality of life was a primary outcome in all studies. Of the 16, five studies compared the QOL between breast cancer survivors and healthy or normal controls.[4,41–44] Two of five also compared QOL outcomes between survivors who have experienced a cancer recurrence to those who have not.[4,43] Three of the 16 studies compared QOL between breast cancer survivors receiving different types of treatment.[2,45,46] Two of the 16 investigated the QOL between breast cancer survivors diagnosed at different ages[47,48]; another two studies compared QOL at time of diagnosis and follow-up[32,49]; and two more examined the impact of treatment on QOL.[50,51] One study looked specifically at the role of ethnicity in QOL outcomes,[52] while the final study examined the impact of length of time since diagnosis on QOL.[53]

Quality of life: In most studies, breast cancer survivors reported a good overall QOL,[32,43,49,51,52] with two of the studies reporting QOL comparable to healthy controls.[4,44] Generally, the longer the time since diagnosis, the better the overall QOL reported,[32,48,52] although a few studies cited no change[46,49] or decreases in QOL[53] over time. Studies comparing QOL between survivors with and without recurring cancers found that those with recurring disease reported worse QOL in some, but not all domains.[4,43,49] With regard to treatment type, some studies report no differences in long-term QOL by treatment type,[45,46,51] while others find significant differences.[2,49] Although univariate analyses revealed that African American women reported lower mean QOL scores than Euro-American women, differences disappeared after multivariate analyses.[52] Ganz,[51] however, reports better QOL outcomes among African American compared to Euro-American women. In the studies reviewed, women reported various concerns in each QOL domain, physical, psychological, social, and spiritual. Findings are reported below according to QOL domains.

Physical quality of life: Eleven of the 16 studies discussed physical domain QOL outcomes for long-term survivors.[2,4,32,41,43,46–51] Generally, survivors report lower physical domain QOL than healthy controls and poorer physical functioning.[4,41,43,49] Arm pain, including swelling, loss of sensation, weakness, and stiffness, are common.[4,32,48,50,51] Survivors also report fatigue,[2,46] with one study finding that younger survivors report the lowest levels of vitality.[51] Physical problems associated with treatment induced menopause are also common.[2,32] One study shows that physical functioning was predicted by age at diagnosis,[48] while another found that older age in general is related to worse physical domain QOL.[47] Another study found that physical health was most affected among women who were both diagnosed with lymphoma and treated with chemotherapy.[2]

Psychological quality of life: Eleven of the 16 studies discussed psychological domain QOL outcomes for long-term survivors.[4,32,41,44,45,47–51,53] Although survivors and controls tend to report similar QOL in most psychological domains,[4] studies report significant psychological concerns among breast cancer survivors including depression and symptoms of Posttraumatic Stress Disorder.[32,41,50,53] Survivors report being overly stressed and worried about the future, and having little control over the world.[32,44]

Table 1. Long-Term Breast Cancer Studies Reviewed

Study	Sample size and type	Time since *dx/tx*	Instruments	Methods (C/L)*
Ahels *et al.*[2]	549 survivors	Mean 10 years	• Quality of Life Cancer Survivors Tool (QOL-CS)	C
Amir and Ramati[41]	39 survivors 39 controls	5 years	• Posttraumatic Stress Disorder (PTSD) • SCL-90 • World Health Organization Quality of Life Assessment (WHOQOL-Bref) • Emotional Distress	C
Ashing-Giwa *et al.*[52]	278 survivors	5 years	• F-36 • Cancer Rehabilitation and Evaluation Survey • Ladder of Life Score • The Life Stress Scale	C
Bloom *et al.*[32]	185 survivors	5 years	• SF-36	L
Broeckel *et al.*[42]	58 survivors 61 controls	Mean 7.65 years	• The Center for Epidemiological Studies, Depression Scale (CES-D) • MOS Marital Functioning Scale • Multidimensional Fatigue Symptom Inventory (MFSI) • Menopausal Symptom Checklist (MSC)	C
Cimprich *et al.*[47]	105 survivors	5 years	• The QOL-Cancer Survivors Instrument	C
Dorval *et al.*[4]	124 survivors 262 controls	Mean 8.8 years	• Physical Health, Functional Status, Psychological Distress (PSI), Social Functioning (MOS Social Support Survey) etc. • Locke–Wallace Marital Adjustment Test	C
Dorval *et al.*[45]	124 survivors	8 years	• Psychiatric Symptom Index (PSI)	L
Fehlauer *et al.*[48]	370 survivors	Median 116 months	• EORTC Quality of Life Questionnaire • EORTC Breast Cancer Module Questionnaire (EORTC QLQ-BR23)	C
Ganz *et al.*[51]	577 survivors	Mean 6 years	• SF-36 • CES-D • Positive and Negative Affect Scale (PANAS) • Sexual Activity Questionnaire (SAQ) • Ladder of Life Score	C

Ganz *et al.*[49]	763 survivors	Mean 6.3 years	• SF-36 • Ladder of Life Score • MOS Social Support Survey • CES-D • PANAS • The Revised Dyadic Adjustment Scale (RDAS) • SAQ • Cancer Rehabilitation and Evaluation Survey • Breast Cancer Prevention Trial (BCPT) Symptom Checklist	L
Helgeson and Tomich[43]	267 survivors 187 controls	Mean 5.5 years	• SF-36 • PANAS • MFSI • Brief Symptom Inventory (BSI) • Dyadic Adjustment Scale (DAS) • Derogatis Sexual Functioning Inventory • Functional Assessment of Chronic Illness Therapy • Impact of Events Scale	L
Holzner *et al.*[53]	87 survivors	Mean 4.7	• EORTC QLQ-C30 • FACT-B	C
Joly *et al.*[46]	119 survivors	9.6 years	• EORTC QLQ-BR23	C
Kornblith *et al.*[50]	153 survivors	Median 20 years	• BSI • EORTC QLQ-C30 • Posttraumatic Stress Disorder Checklist-Civilian • Conditioned Nausea and Vomiting • MOS Social Support Survey	C
Tomich and Helgeson[44]	164 survivors 164 controls	5.5 years	• Functional Assessment of Chronic Illness Therapy (Spiritual Well-being) • SF-36 • PANAS	C

*C = Cross sectional; L = Longitudinal.

Age seems to play a role in a women's psychological reaction to cancer. The poorest mental health outcomes are often found among the youngest survivors.[47,51] Women diagnosed during middle age often report better psychological outcomes and greater general happiness.[47] One study finds that older survivors report less impact of cancer on life plans than younger survivors,[49] while another study finds that older women report greater uncertainty about the future.[47] An additional study found that age at diagnosis modified levels of psychological distress related to type of treatment, finding that for women younger than 50 undergoing partial mastectomy was protective for psychological distress, while for women older than 50 partial mastectomy was associated with high levels of distress.[45] Better mental QOL is associated with fewer chronic conditions, emotional support, feelings of personal control, sense of purpose, fewer physical symptoms, and greater dissatisfaction with medical care.[32,44,50]

Social quality of life: Twelve of the 16 studies discussed social domain QOL outcomes for long-term survivors.[2,4,32,42,45–51,53] Concerns with sexual functioning and satisfaction are the most common issues experienced by survivors, noted in 11 of the 12 studies. Concerns include lack of interest is sexual activity, inability to relax and enjoy sex, difficulty being aroused, difficulty achieving orgasm, and vaginal dryness. One study found that vaginal dryness mediated differences in sexual functioning between survivors and controls.[42] Hormonal and menopausal symptoms are also related to problems with sexual functioning. No changes were found in sexual functioning over time. Other social QOL issues include reduced role functioning, at home, at work and during leisure activities.[2,53] Both sexual and role functioning concerns are aggravated among women who received systemic chemotherapy.[2,49]

Spiritual quality of life: Only four of the 16 studies discussed spiritual domain QOL outcomes for long-term survivors.[32,43,44,47] One suggests that survivors report more faith than controls,[43] while another reports no differences in spirituality between survivors and controls.[44] Cimprich *et al.* reported that older women report fewer positive changes as a result of their cancer diagnosis than did younger women.[47]

5.2. QOL in Long-Term Survivors of Hodgkin's Disease

Study characteristics: In total, five articles, representing four unique studies, met our search criteria for Hodgkin's disease, all published after 1998. Interestingly, all studies were conducted in Europe. The articles are described in Table 2. All studies were cross-sectional and compared Hodgkin's survivors to normal[54–57] or healthy controls.[58] In the studies reviewed, survivors reported various concerns in each QOL domain, physical, psychological, social, and spiritual. Findings are reported below according to QOL domains.

Quality of life: In two of the four studies survivors reported worse overall QOL outcomes compared to controls,[54,55] while two reported no significant differences overall between groups.[56,57] Three of the four studies also QOL compared QOL among survivors receiving different types of primary treatments, finding no significant differences between groups.[54,55,58] Two of the four studies examined differences in QOL due to time elapsed since diagnosis and found no differences [54,55]. Three of the four studies reported that quality of outcomes were worse among older survivors [54,55,58]. One of the four studies reported no differences between men and women,[55] while three others found that women experienced worse physical QOL outcomes than men.[54,55,58]

Table 2. Hodgkin's Studies Reviewed

Study	Sample size and type	Time since *dx/tx*	Instruments	Methods (C/L)*
Gil-Fernandez *et al.*[58]	46 survivors 46 controls	Median 7.6 years	• EORTC QLQ-C30 • Hospital Anxiety and Depression (HAD) Scale	C
Loge *et al.*[54]	459 survivors 2323 controls	Mean 12.2 years	• SF-36	C
Ruffer *et al.*[55]	836 survivors 935 controls	Median 5.2 years	• EORTC QLQ-C30 • LSQ	C
Wettergren *et al.*[57]	121 survivors 236 controls	Mean 14 years	• The Schedule for the Evaluation of the Individual Quality of Life-Direct Weighting (SEIQoL-DW) • HAD Scale • SF-12 • Sense of Coherence (SOC) Scale	C
Wettergren *et al.*[56]	121 survivors 236 controls	Mean 14 years	• SEIQoL-DW	C

*C = Cross sectional; L = Longitudinal.

Physical quality of life: All four studies reported physical QOL outcomes. One of the five found that survivors reported worse QOL scores on all scales, including general health perceptions, physical functioning, role limitations, and vitality, after controlling for age, gender, and education.[54] Another reported that general and physical fatigue was higher among survivors than controls.[55] Increases in reported fatigue were related to systemic symptoms, relapse, and prevalence of tumor disease in the survivor's family.[55] Two of the four studies found that even though survivors and controls reported similar overall QOL outcomes, survivors had poorer physical health perceptions and considered themselves to be in poorer health than controls.[56,58] In one of the two studies, survivors reported lower physical functioning and worse dysnea symptoms.[58] Two of the four studies found that those with more advanced stage of disease had worse QOL outcomes, especially in regard to physical functioning, bodily pain, vitality, and role limitations.[54,56,57]

Psychological quality of life: Three of the four studies reported psychological QOL outcomes. One study reported higher rates of mental fatigue and reduced motivation among survivors than controls.[55] Worse mental fatigue was associated with older age, systematic symptoms, a history of tumor disease in the survivor's family, and the number of tumor disease occurrences in the survivor's family.[55] Although no significant differences in anxiety or depression were found between survivors and controls, one study reported that the anxiety that did exist among survivors was more prevalent among women and those diagnosed with B symptoms than other categories of survivors.[58] Depression was more prevalent among survivors over age 45 at time of study.[58] The third study reported that survivors who rated their financial situation as poor were more likely to rate their mental health as poor when compared to controls.[57]

Social quality of life: One of two studies that reported social QOL outcomes found that survivors reported worse social functioning than controls after controlling for age, gender, and education.[54] The second study found that although survivors perceived their general state of health and overall QOL similarly to controls, survivors reported worse social functioning and more economic difficulties than controls.[58]

Spiritual quality of life: One study reported that survivors were likely to note changes in life perspective due to the illness experience.[56] No other aspects of spirituality were reported.

5.3. QOL in Long-Term Survivors of Prostate Cancer

Study characteristics: In total, 12 studies met our search criteria for long-term QOL issues among prostate cancer survivors. The studies are described in Table 3. Quality of life was a primary outcome in all studies. Of the 12, two studies compared the QOL between prostate cancer survivors and normal controls,[59,60] while a third study compared the QOL of prostate survivors and their partners.[61] Seven of the 12 studies compared QOL outcomes between prostate survivors receiving different primary treatments.[59–65] Ten of the 12 studies examined changes in QOL outcomes over time,[59–68] while the remaining two examined QOL at one point in time.[69,70] Two of the 12 studies looked specifically at the role of ethnicity in QOL outcomes.[63,70]

Quality of life: Overall, issues of urinary, sexual, and bowel dysfunction remain problematic for prostate cancer over the long term. The two studies that compared long-term QOL outcomes between survivors and controls, survivors reported worse problems with urinary and sexual functioning than controls.[59,60] However, in terms of general QOL, results were similar for both groups.[59,60] Of the studies examining changes in QOL over time, all but one[67] reported decreases in sexual functioning. Three studies also reported decreases in urinary function across treatment groups.[60,61,66] Two studies reported decreases in physical functioning and vitality over time.[61,67]

All seven studies comparing long-term QOL outcomes among men receiving different primary treatments detected significant health-related QOL differences.[59–65] Two of the seven, however, reported no significant difference among treatment groups in regard to general QOL.[59,61] Although both of the studies examining the role of ethnicity on QOL outcomes found some differences between African American and Euro-American men, there is disagreement about the specific nature of the differences found.[63,70] Both studies, however, report that African American men were more bothered by their level of sexual functioning than Euro-American men.[63,70] In the studies reviewed, men reported various QOL concerns. Findings are reported below according to four QOL domains.

Physical quality of life: All 12 studies discussed physical domain QOL outcomes for long-term survivors.[59–70] Generally, long-term survivors experience physical problems related to sexual, urinary, and bowel dysfunction. Men experience problems with sexual functioning (e.g., obtaining and maintaining erections)[59–62,64–68,70] and with urinary functioning (e.g., leakage or incontinence).[59–61,64–66,68] Most studies report that severity of specific problems varies according to primary treatment. For example, the findings with regard to bowel functioning vary according to type of primary treatment.[59,62,64,65] One study found that African American men scored lower on the physical component of the SF-36 than Euro-American men.[70] Although one study found that 42% of survivors reported experiencing moderate pain or discomfort in the week prior to the study,[69] others reported no differences in the pain or vitality components of the SF-36 between survivors and controls[60] or among survivors receiving different treatments.[62,64]

Table 3. Prostate Cancer Studies Reviewed

Study	Sample size and type	Time since *dx/tx*	Instruments	Methods (C/L)*
Dalkin *et al.*[66]	1995: 289 survivors 1999: 292 survivors 129 controls	Up to 5 years	• UCLA Prostate Cancer Index (UCLA-PCI)	L
Descazeaud *et al.*[67]	102 survivors	Mean 48 months	• UCLA-PCI • SF-36	L
Galbraith *et al.*[61]	192 survivors	2.5–5.5 years	• QOL • SF-36 • Southwest Oncology Group Prostate Treatment-Specific Symptoms Measure • DAS	L
Hoffman *et al.*[60]	210 survivors 421 controls	5 years	• SF-36 • UCLA-PCI	L
Johnson *et al.*[63]	1433 survivors with radical prostatectomy 642 survivors with radiotherapy	Up to 60 months	• UCLA-PCI	L
Korfage *et al.*[64]	314 survivors	Mean = 52 months	• UCLA-PCI • SF-36 • Euro Qol (EQ-5D) • Sexual Functioning (12 Dutch Single Items)	L
McCammon *et al.*[65]	460 survivors	Range 1–12 years for surgical group 1–22 years for irradiated group	• QOL	C
Miller *et al.*[59]	709 survivors	4–8 years	• SF-12 • Prostate Cancer-Specific QOL (EPIC-26)	L
Penson *et al.*[68]	1288 survivors	Up to 60 months	• UCLA-PCI	L
Potosky *et al.*[62]	1187 survivors	5 years	• General HRQOL • Disease-specific HRQOL • SF-36	L
Sandbloom *et al.*[69]	1243 survivors	Mean 5.7 years	• Euro Qol • BPI	C
Jenkins *et al.*[70]	1112 White 118 African American survivors	Mean 4.3 years	• UCLA-PCI • International Index of Erectile Function • Sexual Self-schema Scale-Male Version	C

*C = Cross sectional; L = Longitudinal.

Psychological quality of life: Seven of the 12 articles discussed psychological domain QOL outcomes.[60–62,64,65,67,70] With regard to the mental health component of QOL, some studies report no differences in SF-36 measures between survivors and controls[60] or among survivors receiving different treatments.[62,64] One study found that African American men scored lower on the mental component of the SF-36 than Euro-American men.[70]

With regard to distress experienced due to specific symptoms, one study reported that survivors reporting urinary dysfunction report higher levels of distress.[62] Another study did not find urinary bother to differ among men with different primary treatments.[65] One study found that although survivors reported being significantly concerned about sexual functioning, few sought treatment.[61] Another cited that even though African American men reported similar or better sexual functioning than Euro-American men,[63,70] the former report higher levels of distress due to sexual functioning.[63,70] African American men, however, were also found to be more likely to seek help for problems with sexual functioning than Euro-American men.[70]

Social quality of life: Seven of the 12 studies discussed social domain QOL outcomes.[60–65,67] In general, studies found no differences in the physical or emotional role components of the SF-36 between survivors and controls[60] or among survivors receiving different treatments.[62,64] One study also found no significant changes in men's physical or emotional role limitations over time.[61] One study reported that although levels of sexual dysfunction are high among most prostate cancer survivors, those who underwent radical prostatectomy experience greater stress on their relationships.[65]

Spiritual quality of life: None of the studies reviewed reported spiritual QOL outcomes from prostate cancer survivors.

Exhibit 1
Major Themes from Literature Review

- Physical domain QOL is the most frequently measured indicator of QOL
- Spiritual domain QOL is the least frequently measured indictor of QOL
- Prostate cancer survivors have worse physical domain long-term QOL than breast cancer and Hodgkin's disease survivors
- Social support appears to decline for all survivor groups
- QOL improves with time since diagnosis for breast cancer survivors, but tends to decrease over time for prostate cancer survivors
- QOL varies according to treatment type received for all survivor groups
- QOL varies according to age for all survivor groups
- Social domain QOL is most commonly impacted by sexual function, especially in the case of breast and prostate cancer survivors

6.0. COMPARISONS OF LONG-TERM EFFECTS OF DIAGNOSIS AND TREATMENT BY CANCER SITE: BREAST CANCER AND HODGKIN'S DISEASE

In this section, we compare two studies conducted by the lead author and her colleagues. The first study was a longitudinal evaluation of physical, social, psychological, and spiritual QOL among long-term survivors of Hodgkin's disease. It was expected that type and frequency of the physical dimension of QOL would be explained by type of treatment, age at the time of treatment and time since diagnosis. It was also expected that social and psychological dimensions of QOL would be explained by differences in educational attainment. The sample was composed of 141 individuals (55% male) who participated in two different surveys conducted at Stanford University Medical Center. The initial interviews were conducted in-person while the 12-year follow-up interviews were self-administered; both surveys were conducted when the individual came to the clinic for a routine check-up. The second study was a 5-year follow-up of a population-based cohort of 185 women who were younger 50 years of age at diagnosis of breast cancer and were cancer-free 5 years later. The initial survey was in-person, often in the women's home, and the 5-year follow-up was a telephone survey.[32] Comparative findings are organized according to Ferrell and colleagues' four domains of QOL.[15,18]

Physical quality of life: Self-reported health ratings and physical health were examined in the Hodgkin's disease cohort. The proportion of who rated their health as "excellent" went up by 10 percentage points; however, the proportion that rated their health from "fair to poor" also went up by 7 percentage points ($p = 0.05$). Similarly, a 10 percentage points increase in physical activity level was found, i.e., the percent of individuals indicating that their physical activity was not compromised (76–66%, $p = 0.02$). The predictors of lower self-ratings of health included being of older age (coefficient is -0.014, $p = 0.05$), being further from treatment (coefficient is -0.05, $p = 0.001$), and reporting greater emotional distress (coefficient is -0.005, $p = 0.05$) while higher educational attainment (coefficient is 0.26, $p = 0.01$) was related to more positive ratings of physical health.

In the breast cancer cohort, little change in the women's ratings of health was reported. Five years after diagnosis, 92% rated their health as good or excellent and only 10% said their health had been getting worse. Significant improvements were reported for surgical symptoms, and the following SF-36 scales (i.e., physical functioning, physical and social roles, vitality, and bodily pain). Overall, physical domain QOL ratings improved when compared to the first year following diagnosis. Using the composite physical measure from the SF-36, a greater increase in physical QOL was associated with reporting fewer chronic conditions (coefficient is -2.60, $p < 0.01$), being employed (coefficient is 3.24, $p = 0.04$), having been treated by chemotherapy (coefficient is 3.88, $p = 0.03$), and fewer children under age 18 living at home (coefficient is -4.77, $p < 0.01$).[32]

Differences between the groups may be due to the greater diversity in age of the Hodgkin's disease cohort, the presence of both men and women, and the longer follow-up for the Hodgkin's cohort.

Psychological quality of life: Few changes in the measures of mental health were expected and, in fact, no change was found on depression as measured by the CES-D,[71] Rosenberg's measure of self-esteem,[72] or on the six subscales of the Profile of Mood States (POMS)[73] in the Hodgkin's disease cohort. A statistically significant higher score ($p = 0.0025$) was found on the total POMS scale, indicating greater emotional distress. The only significant predictor of greater mood distress was time since diagnosis (coefficient is 1.36, $p = 0.01$) while higher self-esteem was marginally related to lower mood distress (coefficient is 5.21, $p = 0.06$).

With regard to the breast cancer survivors, body image problem scores decreased (4.52 to 4.22, $p = 0.01$) by the 5-year follow-up, as did the SF-36 mental health (72.8 to 78.0, $p = 0.001$), and the vitality (50.5 to 62.8, $p = 0.001$) scales. In the multivariate analyses, the mental health dimension derived from the SF-36 was used as an outcome. Significant predictors of a greater increase in mental QOL were fewer chronic conditions (coefficient is -1.66, $p = 0.05$) and a smaller decrease in emotional support (coefficient is 0.38, $p = 0.03$). While the two measures of psychological distress varied in the two studies reducing comparability, it is interesting that the psychological domain of QOL is positively related to the physical domain. As either group's physical functioning improved, so did their emotional functioning.

Social quality of life: Female Hodgkin's disease survivors who were unemployed initially, continued to be unemployed while those who were working at least part-time were more likely to report being employed full-time at follow-up (8.4% increase, although not statistically significant). Male survivors, on the other hand, were more likely to report being unemployed at the second interview. Overall, the unemployment rate of Hodgkin's disease survivors who were over age 30 at the time of treatment increased from 18.8 to 34.1% ($p = 0.03$). Survivors reported that the number of friends and relatives to whom they felt close also was reduced. These constrictions in one's social network could be related to illness imposed restrictions, reduced social activity (lack of employment or not being married, loss of friends due to death) or to stigma. Using multivariate analysis, these different explanations were tested. While the model developed explained 48% of the variance, the only significant variable was the initial number of friends and relatives (coefficient is -0.78, $p < 0.001$). This finding suggests at the time of diagnosis, friends and relatives came to the person's aid, but overtime this "extra" support diminished. With regard to social health, sexual interest had decreased from 19.9 to 49.6% ($p = 0.001$). Multivariate modeling suggests that changes in sexual interest were largely related to increases in emotional distress (coefficient is 0.006, $p < 0.001$) and marginally related to being treated by combined modality treatment (coefficient is 0.156, $p < 0.05$).

We found no significant changes in marital/partner status or in employment status in the breast cancer group. With regard to the SF-36 subscales, social function improved over time. We did not find differences in sexual activity or reporting of sexual problems even though by now most women were menopausal (75% due to treatment) and there were fewer children at home. There were significant decreases in the size of one's social network and emotional support. In multivariate analyses, less reduction in emotional support predicted better QOL.

It is interesting that reductions in survivor's social networks were found in both groups. Employment differences between the female Hodgkin's disease survivors and the breast cancer survivors may be attributed to differences of age at the time of the cancer presentation. Younger women in the Hodgkin's cohort may have had more difficulties in completing their education and developing a career than the breast cancer survivors.

Spiritual quality of life: We measured attendance at religious services in both groups and found no difference in attendance over time. In the breast cancer cohort, we also measured frequency of prayer and again, found no difference over time. We also found that as time post-diagnosis increased, breast cancer survivors' worries about the future also decreased. Eighty-five percent of breast cancer survivors reported that spirituality to be an important part of their lives.

Exhibit 2
QOL in Long-Term Survivors of Hodgkin's Disease and Breast Cancer

Hodgkin's disease	**Breast cancer**
$N = 141$ (55% male) Outcomes at 12-year follow-up	$N = 185$ (100% female) Outcomes at 5-year follow-up
Physical domain • 10% increase in "excellent" self-reported health • 7% increase in "fair" to "poor" self-reported health • 10% increase in physical activity Predictors of low self-rated health include: • older age • longer time since treatment • greater emotional distress • lower educational attainment	*Physical domain* • 10% in "fair" to "poor" self-rated health • Improvements in surgical symptoms, physical functioning, physical and social roles, vitality, and bodily pain Predictors of improvements in physical health include: • reporting fewer chronic conditions • being employed • treatment with chemotherapy • having fewer children at home
Psychological domain • No changes in depression, self-esteem, or mood • Increases in emotional distress Predictors of emotional distress include: • time since diagnosis • lower self-esteem	*Psychological domain* • Improvements in body image, mental health, and vitality Predictors of mental health include: • fewer chronic conditions • smaller decrease in emotional support
Social domain • 15% increase in unemployment • Decrease in social support • 30% decrease in sexual interest Predictors of sexual interest include: • emotional distress • treatment with combined modality	*Social domain* • No changes in employment status or sexual activity • Decrease in social support • Increase in social function Predictors of social domain QOL include: • smaller decreases in emotional support
Spiritual domain • No change in attendance at religious services	*Spiritual domain* • No change in attendance at religious services or frequency of prayer • Decrease in worries about the future

7.0. LONG-TERM EFFECTS OF CANCER DIAGNOSIS AND TREATMENT ON SURVIVORS' FAMILY MEMBERS

The literature on the effect of cancer diagnosis and treatment on family members is sparse.[74] Of studies in this area, most have focused on the impact of cancer soon after diagnosis, during recurrence, or at the terminal phase of the disease.[75–77] One study shows that partners of men with prostate cancer, generally from small convenience samples, report more distress than their sick partners, but also believe that their partners are more distressed. The only reviewed study of long-term prostate cancer survivors found that couples' health-related QOL was associated with marital satisfaction.[61] Distress was inversely related to levels of family support. The men's focus of concern, on their sexual functioning (i.e., impotence), was not shared to an equal degree by their non-sick partners.[78,79] The most relevant study included in our review focusing on family survivorship included families from 1 to 5 years posttreatment,[80] thus making specific statements about the long-term effects of cancer diagnosis and treatment on family members difficult. The study finds that economic resources, marital status, and retirement status for cancer survivors ages 50–70 were related to higher levels of QOL.[80] Contrary to expectations, physical and somatic concerns were unrelated to overall QOL. Social support was positively related to overall QOL while fear of recurrence was negatively related to QOL. The family's meaning of the illness was also related to family QOL.

Few studies have focused on the brothers and sisters of survivors who, themselves, are at higher than average risk for cancer. Most of these studies have focused on siblings at genetic risk.[81–83] Family history of breast or ovarian cancer has been identified as the strongest risk factor for breast cancer. Women who have a sister or other first-degree relative with breast cancer have a 2- to 10-fold increased risk of developing breast cancer themselves.[84,85] And men with a family history of prostate cancer have a 2-fold increased risk. Depending on the age of the relative and whether it is a father or a brother, the risk can be much higher.

Over the past several years, our research team has been studying the long-term reactions of survivors' family members. We have conducted studies of both men and women who have a greater than average risk of breast or prostate cancer due to a family history of the disease and have explored both their psychological and behavioral reactions to their family history of cancer. In this section we present findings from two studies, one with sisters of breast cancer survivors; and the other with the brothers and sons of prostate cancer survivors.

7.1. Sisters of Breast Cancer Survivors Study

In the first of these studies, we interviewed the sister's of women whose breast cancer was diagnosed before age 50.[86] The breast cancer survivors are part of a cohort study discussed previously.[32] Our focus on survivors' sisters rather than their daughters is due to the immediacy of the experience which we thought would make this group more vulnerable and also because the interview presents a teachable moment for an intervention.[87]

Our sample consisted of 163 women, referred by 220 of the breast cancer survivors (76% response rate). In addition to collecting demographic information, we asked them about their breast cancer risk factors to compute a modified Gail index of their actual risk of getting breast cancer, their perceived risk of getting breast cancer themselves given their family history,[82,88] their health status using the MOS SF-36, breast cancer worries[82,88] the intrusiveness of the participants' sisters breast cancer[89] and their breast cancer screening history.

The mean age of the participants was 47. Like their sisters with breast cancer, they were well educated with 75% having some college education; 71% were married and 75% were Euro-American. Most (63%) of the women older than 40 had a mammogram in the past year or three mammograms in the past 5 years, while 75.5% of women of all ages had at least three clinical breast exams in the past 5 years. While 19% had more than one first-degree relative with breast cancer (conferring greater risk), their self-assessed risk of breast cancer ranged from zero to 100% with a mean of 45% while the lifetime risk estimated by the modified Gail model ranged from 6 to 49%, an overestimate of an average of 25 percentage points! Interestingly, only a few women (12%) reported thinking "often" or "a lot" about their chances of getting breast cancer. However, almost a third (31%) reported that they had intrusive thoughts about their sister's diagnosis of breast cancer. Multiple regression analysis determined that the predictors of the woman's self-assessed risk was higher if they had more than one first-degree relative with breast cancer (coefficient is 14.03, $p < 0.01$) or had more intrusive thoughts about their sister's diagnosis (0.16, $p < 0.05$). Having intrusive thoughts also predicted greater breast cancer worries (coefficient is 0.10, $p = 0.0001$) while having a partner or being married predicted fewer worries (coefficient is −0.46, $p = 0.002$). Thus, for sisters of breast cancer survivors, psychological aspect of QOL was affected years later. Perceiving oneself at risk was related to being vigilant about one's own health (i.e., having a mammogram or clinical breast exam).

7.2. Brothers and Sons of Prostate Cancer Survivors Studies

In a study, still underway, 150 African American and 150 Euro-American men ages 35–74 were recruited through relatives whose prostate cancer was reported to the California Cancer Registry between 1997 and 2003.[90] Because of population differences between groups, a random sample (20%) of Euro-American brothers and sons were selected while all eligible brothers and sons of African American men were approached to participate in our study of family members. The initial purpose of this population-based study was to determine the extent to which there are racial/ethic difference between family members (brothers and sons) of African American and Euro-American men in their awareness of their heightened risk of prostate cancer and their use of early detection behaviors. Since a measure of the Gail model has not been developed for prostate cancer, it is not possible to assess the accuracy of risk estimates for prostate cancer.

In a telephone interview, it was determined that the average age of African American men included in the study was 53 years and that of the Euro-American men was 55 years. Statistically significant differences were found on measures of knowledge, preventive behavior, and psychological response to prostate cancer when comparing African American and Euro-American men. Regarding knowledge of prostate cancer, Euro-American were more likely than African American men to report a good understanding of prostate cancer (8.9 compared to 7.3, $p = 0.001$).[90] In regard to preventive behavior, African American men were significantly less likely to have ever had a PSA test (51% versus 75%, $p = 0.0001$) or a digital rectal exam (DRE) (66% compared to 80%, $p = 0.006$).[90] African American men were less likely to perceive their cancer risk; reporting their prostate cancer risk was "higher than average" less often the Euro-American men (35% compared to 65%, $p = 0.0001$).[90] African American men were significantly more likely than Euro-American men to report having greater than average worries about getting prostate cancer (3.9 compared to 3.5, $p = 0.004$). They were also more likely to report health anxiety (18% compared to 16%, $p = 0.003$).[90] African American men also were more likely to agree with the statement that "having a PSA test caused unnecessary worry" about prostate cancer (32% compared to 17%, $p = 0.004$) and were more likely to agree with the statement that "it is pointless to think about prostate cancer since so many things could happen in life" (36% compared to 23%, $p = 0.01$).[90]

While we find that the psychological aspect of brother's and son's QOL was affected to some degree, worries were only reported by some of the men. While there continues to be controversy about the value of PSA testing, these data suggest that both African American and Euro-American men at above average risk for prostate cancer due to family history are inclined to be screened.

Exhibit 3
QOL in Family Members of Long-Term Cancer Survivors

	Brothers and sons of prostate cancer survivors	
Sisters of breast cancer survivors	African American	Euro-American
$N = 163$ Mean age = 47	$N = 150$ Mean age = 53	$N = 150$ Mean age = 54
Preventive health behaviors • 76% obtain CBE[a] • 71% obtain maintenance stage mammography	Preventive health behaviors • 51% ever had PSA[b] • 66% ever had GRE[c]	Preventive health behaviors • 75% ever had PSA[b] • 80% ever had DRE[c]
Average worries	Average worries	Average worries
• 3.7[d] Higher than average risk • 55.6%	• 3.9[d,e] Higher than average risk • 35%[f]	• 3.5[d,e] Higher than average risk • 65%[f]

[a] Clinical Breast Exam.
[b] Prostate-Specific Antigen; Significance of comparison between men $p = 0.0001$.
[c] Digital Rectal Exam; Significance of comparison between men $p = 0.006$.
[d] Possible range 3–12.
[e] Significance of comparison between men $p = 0.004$.
[f] Significance of comparison between men $p = 0.0001$.

8.0. DIRECTIONS FOR FUTURE RESEARCH

Since 1998 when a rigorous review of the published research on long-term survivors was published, a rapid accumulation of research has occurred. In the United States this trend has accelerated since 1997, when the Office of Cancer Survivorship was created in the National Cancer Institute. This event provided greater visibility of the concerns of long-term survivors and funding set asides encourage research in this area. Our review of recent literature on long-term cancer survivors brought home the limitations of this accumulating research and suggests the following directions for future research.

1. *Culture and ethnic/racial effects*: Most of the research focuses on the experiences of either Europeans (all of the Hodgkin's disease studies) or Euro-Americans. Only a few of the studies consider other racial/ethnic or cultural groups. We found one study of breast cancer survivors that compared African American women with Euro-American women and found better QOL among the African American women.[52] Two studies compare African American men to Euro-American men with prostate cancer and found that the former were more likely to seek help for erection problems.[63,70] These three studies suggest that there are cultural differences that need further investigation. Missing from this literature are the long-term effects of cancer on Asian Americans, Hispanics with comparison to either Euro-American or African Americans, and persons from continents other than Europe or North America. Clearly, this is an issue of high concern especially in light of the Institute of Medicine's Report on "Unequal Treatment."[91] If there are disparities in cancer treatment, long-term QOL issues maybe even more significant for these groups.

2. *Family members*: As discussed earlier, there is little literature that focuses on the problems that family members face when their spouse/partner, parent, or sibling is

diagnosed with cancer. What little research that has been done has focused on the time of the initiation of treatment, at the time of recurrence, or during the terminal phase of the disease.[77] All three of the cancer sites reviewed can impact partners of a survivor, but at present there are very few studies on how couples overcome this challenge. In our review, several studies found major changes in sexual functioning even after 5 years after diagnosis. Only few have looked at interventions that can help the couples to deal with this experience.[92–94] Men and women treated for Hodgkin's disease as well as younger women treated for breast cancer may have to cope with infertility. More research should be focused on the impact of cancer survivorship on family members. Interventions for family members who are at higher risk for getting cancer should be a priority as well as interventions to improve family resilience for persons at higher risk for poorer outcomes such as families in which material resources are lower and who are still at the stages of their life where they are balancing work and family roles.

3. *Interventions for site-specific behavioral changes*: As we learn more about the late effects of cancer treatment, interventions are needed to reduce these late effects. For example, research has indicated the multiple benefits of exercise on cancer survivors to improve mood, increase flexibility, maintain weight and bone mineral density. Our literature review did not find many intervention studies, let alone one's whose purpose was to improve the QOL of cancer survivors.

4. *Long-term survivors and work and health insurance issues*: Long-term survivors sometimes have difficulties in maintaining life insurance, health insurance, or full-time jobs that may affect their QOL. This issue is maybe less important for female cancer survivors than in men surviving cancer because a majority of this group of women are married and have a spouse who can request insurance in their own name.[95] Only few of the articles that we reviewed controlled for insurance status. Most of the articles that we reviewed did not control for both the employment status and having health insurance.

5. *Treatment choices and their impact over time*: Especially in the case of breast and prostate cancer, treatment choices must be made at the outset. As indicated earlier, there are clear differences in body image between mastectomy and breast sparing surgery[31] while mortality is the same. There are also differences in physical side-effects for treatment choices that men diagnosed with prostate cancer must make. Given the information on treatment options and the long-term QOL, how much are these men and women participating in choices about the treatments that they receive what kind of choices would informed patients make? In some of our ongoing research, congruence between the desires for participation and actual participation results in different treatment choices and also affects QOL.[96] Clearly, this question is only beginning to be studied in breast cancer and further research is needed, not only for breast cancer treatment decision-making, but also for prostate cancer treatment decision-making.[97,98] As Gotay[3] pointed out there also needs to be more studies identifying those who are in need of support and determining the type of support needed.

9.0. CONCLUSIONS

As cancer diagnosis and treatment continues to improve and cancer survival rates continue to increase, the issues and needs of long-term survivors demand special attention. Our review suggests that long-term survivors of cancer have ongoing issues and concerns associated with diagnosis and treatment. We find that most studies looking at long-term cancer survivors' focus on a narrow view of QOL, often focusing primarily on physical domain issues. We argue that a broader view should be considered; one that examines the four interconnected domains of physical, social, psychological, and spiritual QOL. Although it is true that physical outcomes are important, the psychological, social, and spiritual responses to physical symptoms are equally important and will vary among individuals. A more complete understanding of the long-term impact of a cancer diagnosis and treatment requires inquiry in these additional domains. In addition, few if any of the studies reviewed explored positive outcomes of the cancer experience. There is a clear need to focus on positive aspects of cancer survivorship as well as the negative.

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Chapter 5

Health Care Disparities

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1.0. INTRODUCTION

In the year 2006, health care remains one of the most debated topics in America. At a time when health care costs continue to rise and the availability of health insurance to the population comes at increasing personal cost, ensuring equal and fair access to health care for all remains difficult. It is within this already complex framework that we must try and understand and address as the Institute of Medicine report (IOM) describes, "Unequal Treatment: Confronting racial and ethnic disparities in health care."[1]

The IOM report highlights the disparities for selected cancer sites (lung and bronchus, colon and rectum, female breast, prostate, uterine, cervix, stomach, and liver) that show large variations by race and ethnicity. The exact reasons for these disparities remain unclear but several studies have focused on the possible influence of social, economic, and cultural factors as likely etiologies. The complex interplay among social, economic, and cultural factors as a cause for health care disparity is described in this report and supported by others.[2–4] Determining where in our health care system these problems lie can help elucidate areas of intervention. Most of the research in this area has been related to screening, reactions to diagnoses, and early interventions, this research can provide us with some clues regarding where to look, to understand, manage, and prevent health disparities among cancer survivors. This emerging area of inquiry will improve access and quality of care for all cancer survivors.

2.0. BACKGROUND

There is a difference in cancer survival rates between Caucasians and minorities. African Americans have the highest death rate from all cancers. From data provided by the SEER program shown in Figure 1, for all cancers there is a divergence in death rates between African American patients and Caucasian patients from 1975 to the early 1990s. This gap has since lessened, however it remains larger than it was

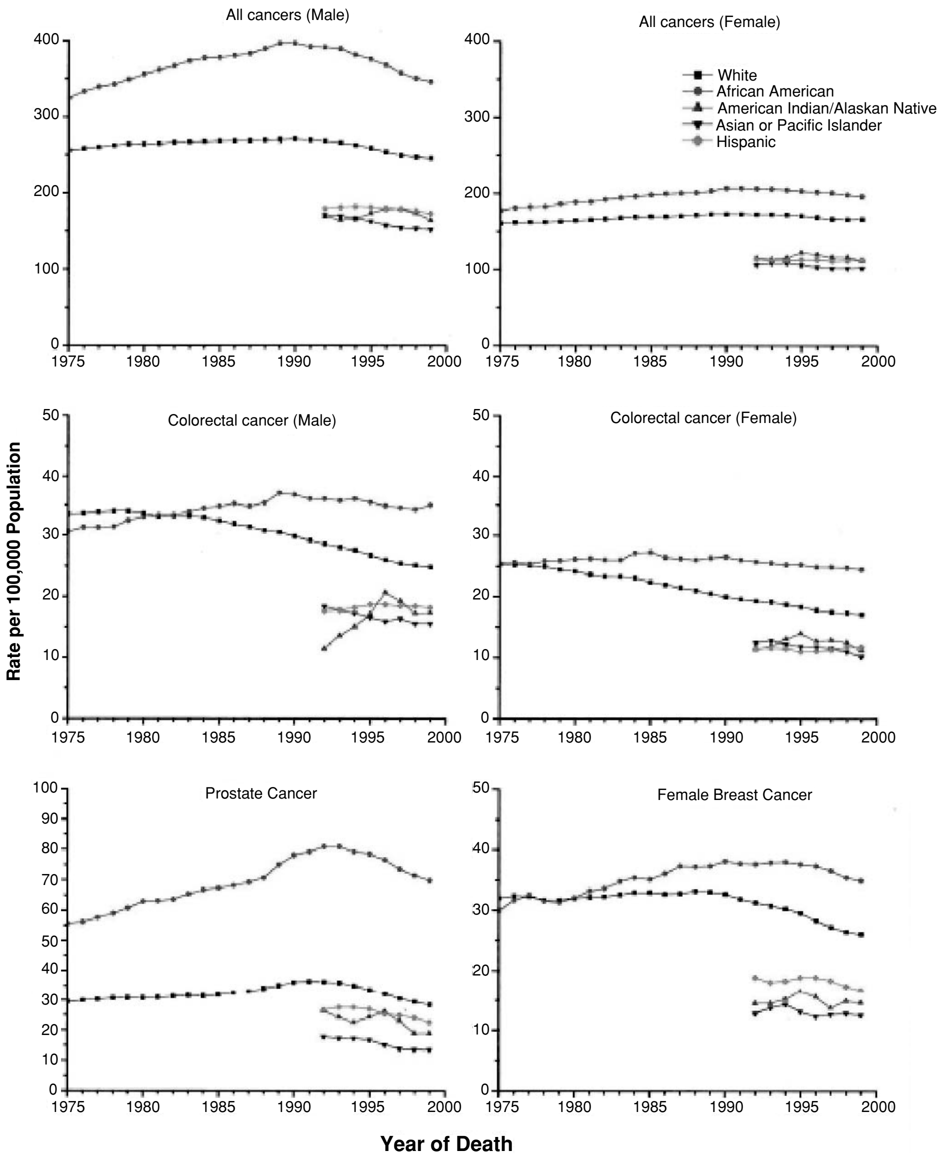

Figure 1. Trends in Mortality for All Combined Cancer, Prostate, Female Breast and Colorectal, by Race and Ethnicity, 1975–2000. (Reprinted with permission from Ward *et al.*[2])

in 1975. A similar trend is seen with death rates from all cancers in relation to race and socioeconomic status.[5,6]

The IOM report showed that there were obvious disparities in health care for minorities in many disciplines of medicine and this disparity extends to cancer. African Americans and other minorities were diagnosed at later stages, had a higher likelihood of having a delay in diagnosis and, even with equivalent treatment, had worse survival rates.[7,8] These disparities are disheartening and closing the gap is an important goal. This goal has already been embraced by the American Cancer Society as one of its challenge goals by the year 2015.

There is an abundance of literature suggesting possible causes for these disparities. These include socioeconomic status,[3,6,9,10] race/ethnicity,[2,7] tumor biology,[11,12] and comorbidities.[13,14] All of these factors contribute to the disparity seen in the mortality from cancer. The impact of these factors on cancer survivors is not well known; only recently have studies on cancer survivors been done. In 1992, a National Health Interview survey was done to examine cancer prevalence and survivorship issues. At that time approximately 6.1% of the adult population or 11 million people reported that they had ever had cancer.[15] Chirikos *et al.* found that breast cancer survivors were more likely than controls to have functional impairments such as lymphedema resulting in decreased work ability, which may affect employment opportunities.[16] Whether differences in these indices of quality of life differ among different racial or ethnic groups ;as not reported however, there is a significant burden of illness among cancer survivors and there is every reason to assume that disparity in access, quality of care, and outcomes contributes to this. While mortality data are available by gender, race, and ethnicity, research is needed to identify the role of these factors among cancer survivors who experience poorer long-term health, and increased loss of productivity.[17]

3.0. SOCIOECONOMIC STATUS

Socioeconomic status (SES) remains the most widely studied variable in the area of health disparity. In many instances it is the most notable difference between Caucasians and minorities. SES is difficult to assess because income level, the most direct assessment of SES, is not routinely obtained when treating cancer patients. As a result SES is a value that must be estimated based on census tract data, patient location, or some other indirect assessment. The significance of SES as a contributing factor to health care disparity has been documented in several studies.[3,6,9,10] Delay in care and decreased utility of surgical intervention are only a few of the outcomes influenced by low SES. Low SES is associated with a lack of resources. According to the US Census Bureau the official poverty rate in 2004 was 12.7%, an increase from 12.5% the year before; this percentage represents 37 million people in the United States. Forty-seven million people in the United States, 15.7%, are without health insurance.[18] The economically disadvantaged are more likely to be uninsured, have less access to health care and are less likely to be informed about their risk for certain diseases.

Poverty itself is a significant impediment to obtaining health care. The 5-year survival rate for people who live in poorer census tract is more than 10% less than that for those who live in more affluent areas[6] and this is shown in Figure 2. Poverty has many negative effects on health and many of these effects are worsened in chronic illnesses such as cancer. Those who are economically disadvantaged are more likely to be undereducated, more likely to have no insurance and more prone to engage in high- risk behavior. If SES is seen as the coalescence of many small barriers into a large possibly insurmountable barrier, then access to health care is the first barrier that must be addressed.

Lack of adequate health insurance is more common among the poor and this results in limited access to care which can manifest as problems in the following areas: screening, stage at diagnosis, and adequacy of treatment. With adequate access to health care patients may obtain preventative screening and diagnostic evaluation when appropriate. The relationship between race, ethnicity, SES, and preventative

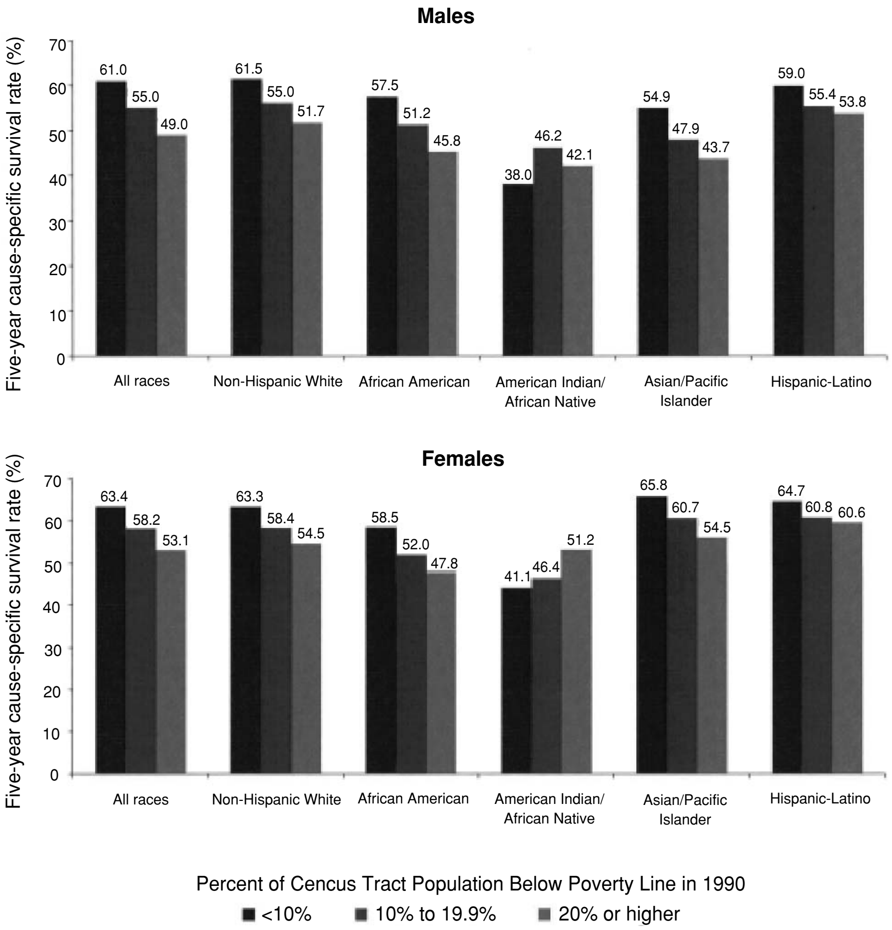

Figure 2. SEER Cancer (All Sites Combined) Survival Among Men and Women, 1988–1994 Patient Cohort. (Reprinted with permission from Ward *et al.*[2])

screening has been well studied. Two well-written review articles from Cancer Causes and Control summarize the literature in this field. People with lower SES are less likely to undergo screening for colorectal cancer and are more likely to be diagnosed at a later stage.[19] A similar literature review for breast cancer was also performed but, difficult to compare given the complex interaction among race, ethnicity, SES, and lack of uniformity between the studies. This review concluded that people with lower SES and breast cancer present at later stages of disease. Also, elder women in lower socioeconomic groups more likely to undergo mastectomy.[20] A recent study by Rosenberg and colleagues showed that health insurance was the socioeconomic variable most associated with regular mammography use even at higher levels of education and SES.[21] In the 1998 data brief by the Commonwealth Fund, a survey on women's health found that not much had changed in the 5 years since a previous study. The rate for screening, though slightly improved, was still lower for minorities than Caucasians; this gap was widest between poor women (income less than $16,000 a year) and women with income greater than $50,000 a year. This survey once again demonstrated that SES remains a significant barrier to adequate and timely screening.[22] Since screening reduces mortality in certain cancers lack of appropriate screening becomes even more important. Mammography for breast cancer reduces mortality by 25% and screening for colon cancer reduces mortality by 20%.[23,24] Lack of adequate screening because of low SES detracts from the mortality benefit derived from screening for these diseases. The second barrier referable to SES is the advanced stage at diagnosis. Numerous studies have shown that African Americans and other minorities present with cancers at a later stage than Caucasians. While tumor aggressiveness and other patient factors may be partly responsible for this phenomenon, delay in diagnosis plays a significant role. A delay in the diagnosis of many cancers affect, the stage at presentation but it is unclear if this results in a survival difference. In two cohort studies of patients with squamous cell carcinoma of the oropharynx, non-white race was a predictor of advanced disease.[25] This delay may be due to the application of screening methods as shown by Cooper *et al.* This study found that African Americans were less likely to undergo screening tests for the diagnosis of colorectal cancer and were more frequently diagnosed at a later stage than Caucasians.[26] The reasons for lack of screening are multiple, most often is secondary to a lack of health insurance due to low SES. The delay in diagnosis and its consequences are best highlighted by breast cancer where the literature on this topic is extensive. Results are conflicting with some studies documenting no statistically significant delay in diagnosis and others showing that African American women do experience a delay in diagnosis and in the initiation of treatment.[27,28] A more recent study by Gwyn *et al.* showed that African American women were more likely than Caucasian women to experience a delay in diagnosis and a delay in treatment.[29]

Once a diagnosis of cancer has been made, obtaining adequate and timely care is the next step in ensuring survival. Numerous studies have examined the relationship between the types of health insurance and the kind of health care obtained. Health insurance may be state funded such as Medicare or Medicaid or private as demonstrated by the multiple health maintenance organizations. In many states the economically disadvantaged are disproportionately taken care of by teaching and/or county hospitals. This has both positive and negative effects. Richardson *et al.* found that Florida teaching hospitals were more likely to diagnose breast cancer in uninsured women, Hispanic women, and those with Medicare/Medicaid than were private hospitals. In addition, they were more likely to receive chemotherapy depending on their stage.[30] Insurance status in itself has been found to be an independent variable in the receipt of guideline therapy, as shown by Voti *et al.* in their study, which reviewed the receipt of standard therapy in Florida based on insurance. Black non-Hispanic women, when compared to white non-Hispanic, were 19% less likely to receive standard therapy and Hispanics 23% less likely. Women on Medicaid and uninsured women were also less likely to receive guideline therapy.[31] This finding is noted on a national level, as seen from the study by Harlan *et al.*, which also documented that the use of guideline therapy was lower in patients who had Medicare or Medicaid as their only source of health insurance.[32] This study also showed that though the number of private and community hospitals outnumber teaching/public hospitals, the latter carry a heavier burden in taking care of the economically disadvantaged.

While access to adequate health care is necessary to ensure optimal treatment of cancer, there are a number of studies that demonstrate that when SES is accounted for differences in cancer survival remain. These differences can be seen in the Department of Defense health care where access to health care is presumably equal.[33]

Socioeconomic status may be the ;ost important factor responsible for the health disparity seen in cancer; however, there are other significant factors. SES is a crude data point that is estimated based on residence, census tract data, and lack of health insurance. These are all used as markers to estimate SES and serve as a basis for comparison of studies.

4.0. RACE AND CULTURE

Race remains a controversial topic in American society. Great strides have been made in eliminating the disparity caused by racism; however, many have argued that the continued use of racial identifiers promotes racism and isolation. In addition, the categories used by the US Census Bureau to define race have been criticized as restrictive because these categories do not take into account the various ethnicities within each category. The use of the term African American or black is broad and does not recognize the diversity within this category such as Caribbean, African and others. In a similar manner, Asian, which has been broadened to include Pacific Islander, encompasses Vietnamese, Chinese, Japanese, Thai, and Indian. Once again it does not show the variety within these groups that has proven to be important in certain instances e.g. the increased incidence of cervical cancer specific to Vietnamese women.[34]

Issues of race in American society also extend to the health care system. In the IOM report there are several studies showing that even when low SES is accounted for, race remains an independent variable in health care delivery disparities. It is difficult to find studies that control for race as an independent factor. Race can be a surrogate for culture, belief systems, social and nutritional habits, and various elements, which are difficult to define and control in studies. Yet in many studies when the data are analyzed using multivariate analysis, certain trends can be seen. There is documented evidence of racial bias noted in several areas of medicine including cancer therapy.

Ayanian *et al.* demonstrated that among Medicare patients the adjusted odds ratio of receiving a revascularization procedure after coronary angiography was 78% higher for whites than blacks.[35] Other studies have demonstrated these racial differences in other kinds of intervention. These findings extend to surgical therapy in cancer. Lathan and colleagues in a study looking at the effect of race on staging and surgery in non-small-cell lung cancer found a similar outcome. This study showed that African Americans were less likely to undergo invasive staging (defined as mediastinoscopy, bronchoscopy, or thoracoscopy) than Caucasians. In addition, once invasive staging had been performed they were less likely to undergo surgical resection. The cohort of patients had access to care via their Medicare eligibility. The reasons for decreased surgical therapy in this study varied.[36] Figure 3 depicts the reasons in this study why surgery was not performed among patients who had undergone invasive staging. A similar outcome was noted in the use of prostatectomy for prostate cancer in African American and Caucasian men[37] and in nonsurgical areas such as the use of standard chemotherapy in adjuvant therapy for colorectal cancer.[38] These studies show that when SES is accounted for, equivalent treatment and outcome is still not attained.

Many studies have documented the role of race in health care disparity. The difficulty when assessing these studies is in determining where this racial bias occurs.

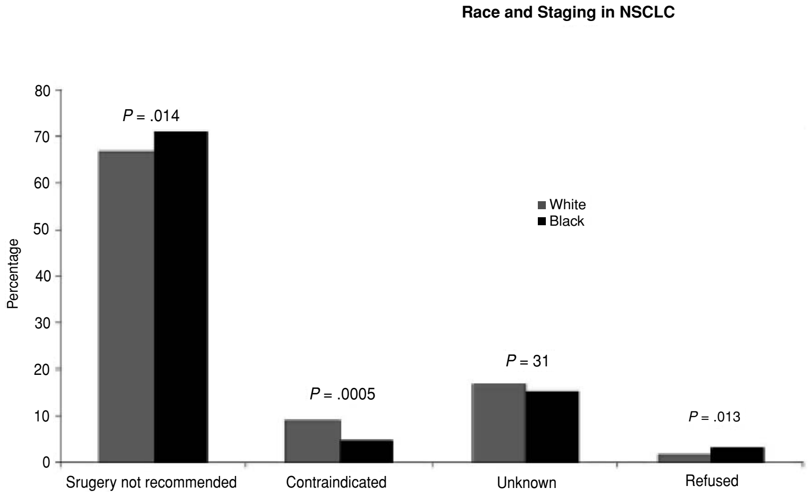

Figure 3. Reasons Recorded in Surveillance, Epidemiology, and End Results for Why Surgery Was Not Performed Among Patients Who Had Invasive Staging. (Reprinted with permission from Lathan *et al.*[36])

There are many areas where it may occur; these include two areas where intervention is possible:;i) treatment facility i.e. teaching versus nonteaching hospital, public versus private hospitals (ii) physician–patient interaction. Individuals bring their life experience, culture, and belief system to all health situations. All these factors influence how the physician and patient interact and what treatments may seem acceptable. These areas should be studied in more detail in order to determine how race and culture impact health disparity. In a retrospective review by Baldwin and colleagues, African American and Caucasian colon cancer patients with Medicare both had an equal opportunity to learn about chemotherapy from a medical oncologist but they did not receive chemotherapy equally.[39] The reasons for this disparity are complex however; this disparity lessens with increasing age and social support, and severity of illness. It is interesting to note that in this study African Americans were more likely to refuse chemotherapy despite an equal number of referrals. The level of educational attainment and SES were predictive factors for refusal of chemotherapy.

Race and culture are often intertwined. Despite this, culture remains the most poorly studied of all the factors that affect cancer survival. Cancer is a diagnosis that affects not only the individual but also his or her entire family. How an individual reacts to the diagnosis, the kind of treatment he or she chooses, and the social support he or she receives is in a large part influenced by their culture. Studies have shown that non-Caucasian women are more likely to have strong beliefs about religious intervention in curing disease or to have a more fatalistic view of cancer.[35,36] Also, as generations are acculturated do we observe differences in health disparities and outcomes across generations? It would be informative to determine how a patient's culture affects their interpretation of their disease and alters their choice of therapy, and their use of self-management techniques. A person's culture may even change his or her approach to long-term health maintenance. From a health care perspective knowing the subtleties in various cultures can only enhance our ability to provide better care for our patients.

5.0. TUMOR BIOLOGY

As the molecular science behind cancer genetics becomes better understood and with all the new data being obtained from the genome project, there is a growing body of evidence to suggest that there may be variations in tumor biology. This may contribute to the health disparity seen among various groups. Some studies have shown that calendar period rather than birth cohort effects are more important to the widening racial disparity.[40] These studies have led to a broader area of research driven by the question "Is there something unique about particular cancers in certain populations that leads to worse prognosis?" This has added to the literature by showing the effect of tumor biology and comorbid conditions on health disparity.

African American women present with breast cancer at a younger age, have poorer prognostic factors such as higher grade, hormone receptor negative tumors, and also present at a later stage when compared to Caucasians.[41–43] It is reasonable to question whether African American women develop more aggressive tumors in breast cancer and if so how can treatment be modified? Recent studies have found differences in the expression of certain genes in breast cancers between Caucasians and African Americans. These differences include alterations in p53 and in e-cadherin and may be associated with more aggressive tumor characteristics.[40,44] In addition, African American women have a higher incidence of hormone receptor negative tumors. This limits the use of hormonal therapy, which has proven very effective in this disease. In the last 20 years, hormonal therapy with Tamoxifen and newer agents such as aromatase inhibitors have been significant additions to the adjuvant therapy armamentarium for hormone receptor positive breast cancer. African American women are likely to have hormone negative tumors and hence are unlikely to benefit from hormonal therapy thereby contributing to the widening mortality gap seen in this disease. Given the increasing sophistication of adjuvant therapy in cancer, molecular differences in various cancers within each group become more important because they may elucidate areas for targeted therapy. These racial differences may impact response to many different interventions, both biologically and behaviorally. There must be further delineation of these differences.

6.0. AREAS OF PROMISING RESEARCH

The impact of comorbidities on cancer survival must be explored. The incidence of various comorbidities varies within different ethnic groups. Knowing which comorbidities affect each group and developing interventions that target specifics groups will enhance survival for all cancer patients. Oncology health care providers must be cognizant of what issues affect each particular racial/ethnic group. A prime example of this is the atypical cancer burden suffered by Asian Americans. As opposed to other racial/ethnic groups, cancer rather than heart disease remains the leading cause of death in Asian Americans.[34] Coupled with the fact that this group also has an increased incidence of cancer caused by infectious agents such as cervical cancer and HPV, hepatocellular cancer and hepatitis B infection, interventions targeted to this group should be focused to address these particular causes.

7.0. SUMMARY

The most important thing about the disparity in cancer survival is that it exists and all health care providers should be aware of this fact. Understanding that there is a problem is the first step in identifying where the problem lies and tackling possible solutions. There is no doubt that research is needed to identify the specific causes for this disparity in cancer survival. This disparity as highlighted in the previous paragraphs includes differences in health care delivery, in access to care and other areas. There is an impressive body of knowledge documenting health disparity among many groups in various cancers. However, many of these studies focus primarily on SES. The ethnobiology also needs to be considered.

In summary, health care disparity in cancer is an area in which there is an ever-increasing body of knowledge. However, there is a need to identify the actual determinants of health care disparity and to distinguish them from those factors with no direct impact. This will become increasingly important as demographics in the United States continue to change. Two goals need to be emphasized in cancer survivorship: we must acknowledge the existence of these ;isparities, and we must also take active steps to reduce and eliminate this phenomenon. Only continued, focused research in this field will achieve these goals.

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Chapter 6

Measuring Quality of Life in Cancer Survivors

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1.0. INTRODUCTION

Over the past 15 years there has been a steady decline in cancer-related deaths in the United States. Although more than a million people are diagnosed with cancer annually, over half are estimated to live at least 5 years beyond their initial diagnosis.[1] Roughly 3% of the U.S. population has survived cancer (about 10 million people), with nearly a million of these people living some 20 years after their diagnosis.[2] Combined, these trends suggest that more people are living with or beyond cancer than ever before. Despite these promising developments, the quality of a cancer survivor's life remains affected well past the completion of treatment. Health care professionals are continually challenged to better understand how cancer has impacted a person's life and provide assistance in navigating the complex maze often inherent to survivorship.[3–6,7–14]

Due in part to improved therapeutic agents and supportive care regimens, attention to the enduring effects of cancer and its treatment has grown increasingly over the past two decades. Although empirical studies have documented the delayed negative impact of cancer and its treatment across physical and psychosocial domains, there are several limitations with this body of research. First, few studies have evaluated long-term survivorship (e.g., greater than 10 years). Related to this, little emphasis has been placed on lifespan development as it is affected by cancer. Further, the overall lack of emphasis on positive outcomes that encompass World Health Organization (WHO) criteria (e.g., physical, mental, and social well-being) additionally limits our ability to understand potential personal benefits that might accrue from successful cancer therapy, effectively promoting positive health among survivors. Finally, most previous research has overwhelmingly been retrospective and cross-sectional, without sufficient consideration of internal and external factors such as comorbid physical and mental problems and health care delivery issues ranging from health insurance and employment to disability rights of survivors. Excluding factors such as these has widespread policy-based ramifications in terms of informing best practices and health care delivery improvement as a whole.[15]

A small but growing body of research has enhanced the understanding of perceived benefits and positive outcomes of long-term cancer survivors and suggests that quality of life (QOL) can be improved through confronting and surviving the normal, often unpleasant sequelae from diagnosis through treatment and beyond. In addition to the assessment of negative aspects of QOL, new approaches have begun to incorporate the measurement of constructs such as positive change, stress-related growth, posttraumatic growth, thriving, and positive benefits.[16–18]

In this chapter, we define "cancer survivor" according to the definition set forth by the National Cancer Institute's Office of Cancer Survivorship: "an individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends, and caregivers are also impacted by the survivorship experience and are therefore included in this definition."[2] This definition is inclusive of people who are currently no longer receiving treatment or have no current or active disease as well as people with advanced stage cancers (e.g., lung and prostate) who may continue to live for a significant period of time as self-identified "disease free" survivors. The purpose of this chapter is to highlight the spectrum of health-related quality of life (HRQL) issues cancer survivors commonly encounter with specific focus on the measurement of these issues. State-of-the-art science in this area will be reviewed, including special attention to conceptualization of HRQL domains as well as innovative methodologies and delivery platforms of which members of our research group have contributed significantly. From this synthesis, we will present recommendations for future research directions and applications that can have lasting effects on the well-being of cancer survivors.

2.0. SURVIVORSHIP ISSUES AND HRQL

Cancer survivors report numerous positive and negative outcomes related to their cancer. The prevailing model of multidimensional health status, originally put forth by the charter of the WHO, defines health as "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity."[19(p.100)] The late effects of cancer can also be classified under these three dimensions, with definable subsets of measurable concepts, or latent traits, found within each dimension (Figure 1). From our review of the literature[12,20–27] and empirical work over the past 15 years[24,27–46] we have built upon this fundamental framework of self-reported health, preserving the original.

To understand the magnitude of HRQL issues among cancer survivors, we have classified these concepts into discrete domains, however it is understood that they represent a highly interrelated and dynamic system. Adhering to this model of self-reported health, the late effects of cancer can have wide spread ramifications. For example, many of the late physical effects (e.g., pain, fatigue, urinary incontinence, infertility) can also have significant emotional and social consequences. Since those with increasing age also represent a large segment of cancer survivors, it is sometimes difficult to determine whether physical changes are predominantly age or cancer related (e.g., fatigue, decreased libido, weakness). Apart from the observed physical changes, the psychosocial and existential issues acknowledged by survivors

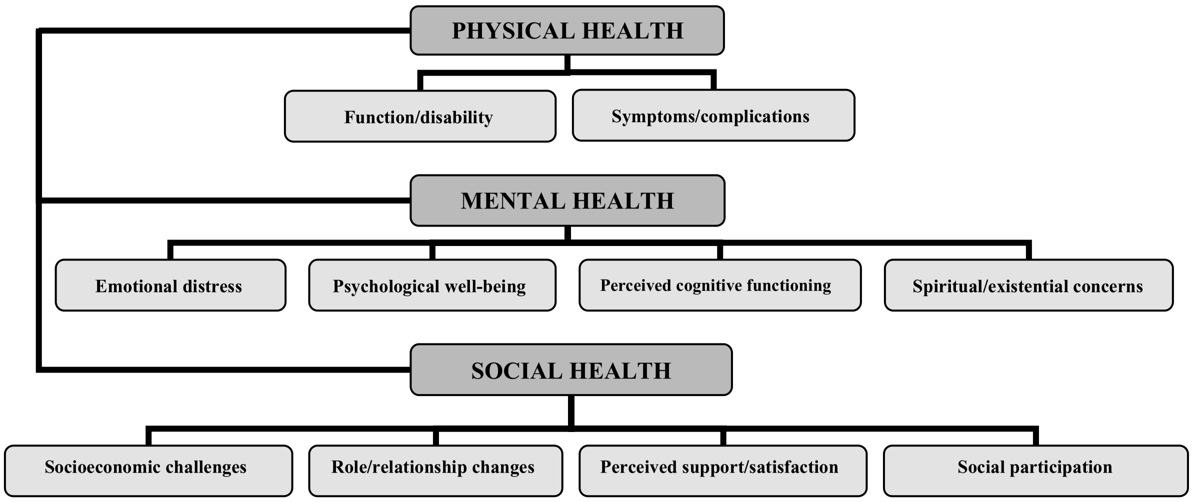


Figure 1. Conceptual Framework of Health-Related Quality of Life and Cancer Survivors.

appear to be directly linked to the experience of cancer. Survivors frequently describe apprehension, unease, and heightened vulnerability related to the possibility of a recurrence or that their bodies are somehow defective and have failed them.

Depending on myriad internal and external factors (e.g., personality style, environmental facilitators or inhibitors) being a cancer survivor can have advantageous or obstructive consequences, such as inspiring one to appreciate life to the fullest or become immobilized with fear of the future. Because of the numerous mental, physical, and social changes many cancer survivors experience years following their treatment, ongoing HRQL assessment becomes critical. Such assessment can serve as a useful gauge of treatment success, assist in the identification of long-term complications that should continue to be monitored by medical personnel, or identify potential teaching and learning moments where health promotion interventions could be implemented.[6] The following section provides an overview of measures commonly used to assess HRQL in cancer survivors.

3.0. HRQL MEASURES AND CANCER SURVIVORS

Both generic- and cancer-specific HRQL measures have been administered to heterogeneous and homogeneous samples of cancer survivors. Tables 1–3 provide a comprehensive list of frequently used measures with specific symptoms and HRQL domains and are included to help the user begin to select appropriate instruments for their purpose. While most investigators' needs can be more or less met by several of the available instruments, these tables enable one to consider coverage of the concepts of interest in a planned research or clinical program. This is followed by a brief review of these measures and their measurement characteristics, such as reliability and validity. The majority of these measures have been used in survivorship studies. A small group of additional measures has not been frequently used with cancer survivors, but have been included because they measure important content areas that are relevant to the survivorship experience.

3.1. Common Measurement Characteristics of Quality of Life Scales

Three basic measurement characteristics found in a good assessment tool are reliability, validity, and responsiveness.[47–49] Reliability is primarily concerned with the stability of items within a test and the uniformity between test scores over time. Two common forms of test reliability are internal consistency (how well items "hang together") and test–retest reliability (the stability of scores over repeated measurements). Test validity deals with the degree to which an instrument accurately measures what it claims to measure. Several types of validity evidence can be examined, such as face validity (degree to which the scale appears to measure the intended domain), content validity (how well test items qualitatively represent the actual content area of study), and criterion validity (how well an instrument's scores correlate with a "gold standard"). Two types of criterion validity are concurrent and predictive (or known-groups) validity. Another type of validity is construct validity (how well test items reflect the latent variable(s) in question), which can be measured through convergent or discriminant associations with other variables. Finally, responsiveness exists when a measure detects QOL changes as a result of disease or treatment.[47–49]

Table 1. Physical Health Issues for Cancer Survivors Across Select Patient Reported Outcome Measures

		Activities of Daily Living	Benefit Finding Scale	Brief Symptom Inventory	Cancer Rehabilitation Evaluation System	Cancer Worry Scale	Center for Epidemiologic Studies Depression	COPE Scale	Dyadic Adjustment Scale	EORTC Quality of Life Questionnaire-Core	Ferrans and Powers QOL Index	Functional Assessment of Cancer Therapy	Functional Living Index Cancer	HOPE Scale	Impact of Events Scale	Instrumental Activities of Daily Living	Long-Term Quality of Life	Medical Outcomes Study short forms:	Memorial Symptom Assessment Scale	Nottingham Health Profile	Profile of Mood States	Psychosocial Adjustment to Illness Scale	Quality of Life-Cancer Survivors	Quality of Life in Adult Cancer Survivors	Rotterdam Symptom Checklist	Sexual Activity Questionnaire	Spitzer Quality of Life Index	UCLA Prostate Cancer Index
Function and disability	ADLs	×			×	×				×	×	×	×					×		×							×	
	Bowel/bladder				×					×		×							×				×		×			×
	IADLs				×				×	×		×	×			×		×				×					×	
	Mobility/ambulation				×					×		×						×		×								
	Oral expression									×		×																
	Sexual activity				×				×	×	×	×							×			×	×	×	×	×		×
Symptoms and complications	Alopecia		×		×					×		×							×						×			
	Appetite/weight			×	×		×			×		×					×		×				×		×			
	Auditory problems									×		×																
	Bloated sensation									×		×							×									
	Cramps/stiffness											×																
	Dizziness			×								×							×						×			
	Dry mouth									×		×							×						×			
	Fatigue/energy			×	×					×	×	×		×			×	×	×	×	×	×	×	×	×	×	×	
	Headache									×		×													×			
	Hormonal change									×		×											×					
	Indigestion									×		×																
	Infertility									×		×											×					
	Skin problems									×									×									
	Lymphedema and swelling									×		×							×									
	Mouth sores											×							×									
	Musculoskeletal									×		×																
	Nausea/vomiting			×	×					×		×	×						×				×		×			
	Numbness/tingling			×						×		×					×		×				×		×			
	Pain and discomfort			×	×					×	×	×	×				×	×	×	×			×	×	×	×		×
	Olfactory changes									×		×																
	Shortness of breath			×						×		×							×						×			
	Sleep problems			×	×		×	×		×		×			×				×	×			×		×			
	Swallowing difficulty				×					×		×							×						×			
	Sweats									×		×							×									
	Taste changes				×					×		×							×									
	Tremors											×																
	Visual problems									×		×					×											

Table 2. Mental Health Issues for Cancer Survivors Across Select Patient Reported Outcome Measures

		Affect Balance Scale	Benefit Finding Scale	Brief Symptom Inventory	Cancer Rehabilitation Evaluation System	Cancer Worry Scale	Center for Epidemiologic Studies Depression	COPE Scale	Dyadic Adjustment Scale	EORTC Quality of Life Questionnaire-Core	Ferrans and Powers QOL Index	Functional Assessment of Cancer Therapy	Functional Living Index Cancer	Goal Interference Scale	HOPE Scale	Hospital Anxiety and Depression Scale	Impact of Events Scale	Life Orientation Test-Revised	Long-Term Quality of Life	Medical Outcomes Study short forms:	Memorial Symptom Assessment Scale	Mental Adjustment to Cancer Scale	Nottingham Health Profile	Posttraumatic Growth Inventory	Posttraumatic Stress Disorder Checklist	Profile of Mood States	Psychosocial Adjustment to Illness Scale	Quality of Life-Cancer Survivors	Quality of Life in Adult Cancer Survivors	Rotterdam Sy mptom Checklist	Spitzer Quality of Life Index
Emotional Distress	Body Image Issues				×					×	×	×	×								×						×	×	×		
	Fear, Uncertainty, Vulnerability			×	×	×	×			×		×	×			×			×			×				×		×	×		×
	Hardship/Hassle				×							×	×																		
	Irritability/Anger			×	×			×		×		×									×	×	×		×	×	×			×	
	Posttraumatic Stress																×								×						
	Psychosis			×																											
	Sadness/Depression	×		×	×		×			×		×	×							×	×	×	×			×	×	×	×	×	×
	Survivorship Guilt																											×			
	Worry/Anxiety	×		×	×	×	×			×	×	×	×		×	×				×	×	×	×			×	×	×	×	×	×
Psychological Well–being	Assertiveness				×							×																			
	Coping		×					×				×	×									×						×	×		
	Fighting Spirit											×										×									
	Happiness/Well-being						×				×	×	×							×				×		×		×	×		×
	Healthcare Efficacy																		×			×									
	Mastery & Control				×			×			×	×			×	×			×			×	×	×				×			×
	Optimism						×					×	×		×			×				×					×		×		
	Posttraumatic Growth							×				×							×			×						×	×		
Cognitive Function	Attention Problems			×	×		×					×									×				×	×		×	×		
	Confusion																									×					×
	Executive Function			×								×																			
	Memory Difficulty			×	×					×		×													×	×		×	×		
Spiritual & Existential Concerns	Acceptance/Patience		×					×				×																			
	End of Life Issues	×			×							×																	×		
	Goal/Value Shifting							×				×		×	×							×									
	Life Satisfaction and Appreciation						×				×	×			×	×			×			×		×				×	×		
	Sense of Meaning & Purpose		×								×	×				×			×			×		×				×	×		
	Spirituality		×					×	×	×		×							×			×		×				×			
	Time Orientation Changes																					×									

Table 3. Social Health Issues for Cancer Survivors Across Select Patient Reported Outcome Measures

	Socioeconomic challenges		Role and relationship changes				Perceived support and satisfaction				Participation	
	Financial strain	Occupational and career changes	Altruism and involvement	Isolation and alienation	Relationship changes	Role changes	Caregiver burden guilt	Discrimination and stigma	Healthcare satisfaction	Perceived social support	Recreation/leisure	Socialization
Affect Balance Scale				×								
Benefit Finding Scale			×		×							
Brief Symptom Inventory				×	×			×				
Cancer Rehabilitation Evaluation System	×	×		×	×	×		×		×	×	
Center for Epidemiologic Studies Depression				×						×		
COPE Scale		×								×		
Duke-UNC Functional Social Support										×		
Dyadic Adjustment Scale	×	×			×					×	×	
EORTC Quality of Life Quesionnaire-Core	×	×		×	×				×	×	×	×
Ferrans and Powers QOL Index		×			×	×				×		
Functional Assessment of Cancer Therapy	×	×	×	×	×	×	×	×	×	×		
Functional Living Index Cancer				×							×	
Long-Term Quality of Life			×		×						×	×
Medical Outcomes Study short forms:		×			×	×						
Mental Adjustment to Cancer Scale										×		
Nottingham Health Profile				×			×			×		
Posttraumatic Growth Inventory			×		×					×		
Psychosocial Adjustment to Illness Scale	×	×		×	×				×	×	×	×
Quality of Life-Cancer Survivors	×	×		×	×				×			
Quality of Life in Adult Cancer Survivors	×			×	×			×				×
Spitzer Quality of Life Index		×								×		
UCLA Prostate Cancer Index									×			

3.2. Generic Measures

Affect Balance Scale (ABS).[50,51] The ABS was developed to measure psychological well-being and contains 10 items; five that deal with positive affect and five that deal with negative affect. It has been used in a variety of settings and populations, including cancer survivors.[52,53] Respondents are instructed to focus on their feelings during the past few weeks and reply with a yes (positive) or no (negative) answer. A Positive Affect Scale score (range from 0 to 5) is computed by summing the five positive affect items; a Negative Affect Scale score (range from 0 to 5) is obtained by summing the five negative affect questions. A total score (range from 0 to 10) is computed by subtracting negative affect scale scores from positive affect scale scores and adding five.

Brief Symptom Inventory-53 (BSI).[54] The BSI-53 is a 53-item scale reflecting nine symptom dimensions, including somatization, obsessive–compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism.[54] Respondent psychological distress is calculated through subscale and global scores, which distinguish emotional from physical aspects of distress. This distinction is useful in oncology settings where it can be convenient to separate psychological from disease- or treatment-related effects. It has been used extensively with cancer patient samples, including survivors of breast cancer[55–57] and pediatric sarcoma[58] and mixed samples.[59,60] Scores have demonstrated adequate internal consistency (Cronbach's alpha = 0.71–0.85) and test–retest reliability (Pearson's $r = 0.68-0.91$). Convergent and criterion-related validity has also been reported with cancer samples.

Center for Epidemiological Studies-Depression Scale (CES-D).[61] The CES-D is a 20-item self-administered inventory designed to assess depression in the general population. The scale is comprised of four subscales: somatic-retarded activity, depressed affect, positive affect, and interpersonal relations. Adequate reliability (Cronbach's alpha = 0.84–0.90; test–retest = 0.51–0.67) and validity (known groups, concurrent, discriminant) have been reported.[61] The CES-D has been used with a variety of medically ill populations, including cancer survivors such as bone marrow transplant,[53] breast,[62–65] and lung.[66]

Dispositional Hope Scale (DHS).[67] The DHS is a 12-item self-report measure of hope; four items are characterized by "agency for goals," four reflect "pathways toward goals," and four are distracters (not scored). Scores are rated on an 8-point continuum (1 = definitely false; 8 = definitely true). Adequate internal consistency reliability has been reported (Cronbach's alpha = 0.80) as well as construct, discriminant, and convergent validity.[67,68]

Duke-UNC Functional Social Support Questionnaire (FSSQ).[69] The FSSQ is an 8-item self-report measure of perceived functional support with medical patients. Originally organized into four support subscales (confidant, affective, instrumental, and quantity), factor analysis yielded two cohesive factors: Confidant support (5 items) and Affective support (3 items). Respondents rate each item on a 5-point scale from 1 (much less than I would like) to 5 (as much as I would like), with higher scores indicating higher perceived support. The scale has acceptable test–retest reliability (Pearson's $r = 0.66$) and item–remainder correlations were used to assess internal consistency (Pearson's $r = 0.50–0.85$). It has also demonstrated adequate construct, concurrent, and discriminant validity.[69–72] This scale has been used in research with breast cancer survivors.[73]

Dyadic Adjustment Scale (DAS).[74] The DAS is a 32-item scale designed to measure the quality of marital relationships. The measure consists of the following subscales:

Dyadic Consensus, Dyadic Satisfaction, Dyadic Cohesion, and Affectional Expression. Cronbach's alpha coefficients for the subscales were 0.90, 0.94, 0.86, 0.73, respectively. Coefficient alpha for the total scale was 0.96. Each of the scale's items has been found to correlate significantly with marital status among a sample including both married and divorced individuals. The DAS is significantly and highly correlated with another widely-used scale of marital adjustment[74] and has been used in previous research with cancer patients, e.g.,[75–78] and cancer survivors.[65]

Goal Interference Scale (GIS).[40,79] The GIS is a 20-item self-report assessment tool that measures the extent to which one's disease and/or treatment has interfered with progress on personal projects (e.g., personal, family, health, career/work). Respondents are instructed to list as many personal projects they are engaged in at the present time (and have been over the past 2 months) and choose the four most important ones, ranking them from 1 (most important) to 4 (least important). Next, a series of questions probes the extent and speed of their progress, including how satisfied they are with their progress/effort and how meaningful these projects are to them. Used with cancer patients, the psychometric properties of the GIS appear to be quite good, with good internal consistency reliability (0.89), convergent validity, and known groups validity.[40,79]

Hospital Anxiety and Depression Scale (HADS).[80] The HADS is a 14-item self-report assessment tool that measures anxiety and depression. It has been used extensively in oncology settings for screening and clinical research purposes.[81–89] Although several studies have found the HADS to have sound psychometric properties in cancer studies,[82,86,87] it has been reported that it may be insensitive to differentiate anxiety and depression among cancer patients; therefore, some have called for its use as a global measure of distress.[82,83,85]

Impact of Event Scale (IES).[90] The IES is a 15-item self-report scale designed to measure two major psychological responses to stressful life events: avoidance and intrusion. The respondent reports the frequency of experiencing either avoidance or intrusion of specified thoughts during the past 7 days. Subscale scores are calculated for Intrusion (7 items; alpha = 0.78) and Avoidance (8 items; alpha = 0.82). Split-half reliability of the total scale is 0.86.[90] The IES has been used extensively in studies with cancer patients[59,91] and cancer survivors.[55,92,93]

Instrumental Activities of Daily Living Scale (IADL).[94] The IADL questionnaire assess the extent to which a person needs assistance in completing eight tasks related to living independently: using the telephone, accessing transportation, shopping, food preparation, housekeeping/handyman work, doing laundry, taking medications, and managing finances.[94] The three possible responses to each category include: require assistance to perform the task (one point each), require some assistance to perform the task (zero points), and unable to do the task (zero points). Although this has been used with cancer survivors[95] it is less sensitive due to ceiling effects.

Katz Index of Independence in Activities of Daily Living (KI-ADL).[96] The KI-ADL assesses performance in six areas of physical functioning: bathing, dressing, toileting, transferring, continence, and feeding. Scored yes or no for independence in each area, a six indicates full functioning; a four indicates moderate impairment and a score of two indicates severe impairment of functioning. Correlating highly with measures of physical functioning, these scores can be less sensitive with cancer populations because of ceiling effects.

Life Orientation Test-Revised (LOT-R).[98] The LOT-R is a 10-item self-report measure (6 target items; 4 fillers) designed to assess individual differences in dispositional optimism and pessimism. Ratings are made on a 5-point Likert scale that ranges from “I agree a lot” (1) to “I disagree a lot” (5). In past research with cancer patients, it has shown good reliability (Cronbach’s alpha = 0.78) and construct validity.[98]

Medical Outcomes Study Short-Forms 12 & 36 Health Survey (SF-12 & SF-36).[99–101] The SF-36 is a generic self-report instrument used to assess QOL. It is comprised of eight subscales: physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions. The SF-12 is a 12-item short-form health survey derived from the longer SF-36 instrument and encompasses the same eight dimensions with fewer items.[99] Convergent validity and reliability characteristics of the SF-36 have been well established (Cronbach’s alpha = 0.78–0.93). The SF-36 has previously been used with cancer patients as well as cancer survivors, including breast[63,102] and lung cancer.[103]

Nottingham Health Profile (NHP).[104] The NHP is a 38-item self-report questionnaire that measures subjective health status across the following domains: pain, emotional reactions, sleep, social isolation, energy, and physical mobility. Responses are based on yes/no statements about ones life. Good reliability evidence has been reported in other medical conditions (Cronbach’s alpha = 0.68–0.74; 0.63–0.80).[105–108]

Posttraumatic Growth Inventory (PTGI).[109] The PTGI is a 21-item scale designed to assess a person’s perception of benefit related to experiencing a traumatic event. Respondents are asked to rate the degree to which they experienced a positive change on a scale from zero to five. Factor analysis revealed five possible subscales (New possibilities, Relating to others, Personal strength, Spiritual change, and Appreciation of life)—each demonstrating adequate internal consistency (Cronbach’s alpha = 0.67–0.85) in addition to the total score (Cronbach’s alpha = 0.90). Construct validity has been reported by the scale’s authors. It has been used in several cancer survivor studies, including hematologic,[16] breast,[18,63] and prostate.[110]

Posttraumatic Stress Disorder Checklist-Civilian (PCL-C).[111] The PCL-C is a 17-item self-report scale that corresponds to criteria B, C, and D for posttraumatic stress disorder of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Items from three symptom clusters (reexperiencing, numbing/avoidance, and hyperarousal) are rated on a 5-point scale based on experiences over the past month. Used in survivor studies with bone marrow transplantation,[112] and breast cancer,[56,113,114] the PCL-C has demonstrated good internal consistency reliability (Cronbach’s alpha = 0.93) and construct validity.[111,115]

Profile of Mood States—Short Form (POMS-SF).[116] The POMS-SF is a 30-item measure of recent affective state. It yields a total mood disturbance score as well as subscale score for depression, tension, confusion, anger, fatigue, and vigor. Individual subscale alpha coefficients have been reported to be: depression (0.81–0.83), tension (0.86–0.88), confusion (0.75–0.79), anger (0.87–0.89), fatigue (0.89–0.91), and vigor (0.89–0.90).[116] The POMS has been used extensively in studies of BMT patients.[117–119] It has been used extensively in survivorship studies, including breast,[120–124] and prostate.[125,126]

Psychological Adjustment to Illness Scale—Self Report (PAIS-SR).[127] The PAIS-SR is a 46-item self-report scale that measures psychosocial adjustment across seven subscales: health orientation, vocational environment, domestic environment, sexual relationship, extended family environment, social environment, and psychological distress. Using a 4-point rating scale, respondents are instructed to indicate whether they have no problems (0) or multiple problems (3). Internal consistency (Cronbach’s alpha) for PAIS-SR scores ranged between 0.68 and 0.93 in a sample of lung and mixed cancer patients.[127] Construct validity was also reported for the PAIS-SR, which has been used in a variety of survivorship studies.[128–130]

Spitzer Quality of Life Index—Patient Version (QL-I).[131] The QL-I is a 5-item QOL index designed to assess QOL domains such as health, activity, daily living, support, and outlook. Originally designed as a physician-rated measure, it is also now used as a patient reported outcome. Questions are rated on a 3-point scale (0–2) and has been used in cancer studies. It has demonstrated discriminant validity as well as satisfactory internal consistency reliability (Cronbach's alpha = 0.78).[131]

3.3. Cancer-Specific Measures

Benefit Finding Scale (BFS, 17 item version).[14,132] The BFS is a 17-item scale that measures the perceived positive contributions of being diagnosed and treated for breast cancer. Originally developed by Tomich and Helgeson[14] this version includes additional items reflecting global positive domains. Responses are rated on a 5-point scale ranging from "I disagree a lot" to "I agree a lot" with items reflecting global positive domains (acceptance, interpersonal growth, sense of purpose, spiritual growth, priorities, becoming a stronger person, realizing support from friends) as well as concrete qualities (time management, renewing interest in activities, and family involvement). Forming a single factor, scores have demonstrated strong internal consistency (Cronbach's alpha = 0.95). Although studies are mixed, some preliminary evidence suggests that earlier benefit finding predicts long-term psychosocial adjustment.

Cancer Rehabilitation Evaluation System (CARES).[133,1134] The CARES is a 139-item self-administered rehabilitation and QOL instrument, while the CARES-Short Form (CARES-SF) contains 59 items. Both are highly correlated (Pearson's $r = 0.98$)[134] and are comprised of a list of statements reflecting problems encountered by cancer patients. They produce five summary scores reflecting physical, psychosocial, medical interaction, marital, and sexual dimensions, and a total score. The CARES predicts extent of disease in colorectal and lung cancer patients and has been found to discriminate between extensive disease and no evidence of disease in prostate cancer patients. Ganz *et al.*[133] also demonstrated the sensitivity of the CARES to improvement in QOL in breast cancer patients over a 13-month period. Used with a wide variety of cancer survivor samples including breast,[102,120,121,133,135,1136] prostate,[136,137] and mixed,[138] adequate test–retest reliability, internal consistency (Cronbach's alpha = 0.88), and concurrent validity has also been reported.[133,134,139]

Coping Orientations to Problems Experienced Inventory (COPE).[140] The COPE is a theoretically based, 60-item self-report inventory that assesses a variety of coping strategies, from functional to dysfunctional.[140] Consisting of three primary item groupings (problem focused, emotional focused, and dysfunctional), scales include: active coping, planning, restraint coping, instrumental and emotional support seeking, suppression of competing activities, positive reinterpretation, religion, humor, acceptance, emotional venting, denial, behavioral and mental disengagement, and substance use. Respondents are asked to rate the degree to which they typically use each coping strategy when under stress. Ratings are made on a 4-point Likert scale that ranges from "I haven't been doing this at all" (1) to "I've been doing this a lot" (4). Shortened to 28 items, the Brief COPE scale measures these 14 subscales and has demonstrated good internal consistency (Cronbach's alpha = 0.50–0.90) and has demonstrated good construct validity.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—CORE 30 (EORTC QLQ-C30).[141] The EORTC QLQ-C30 measures physical, role, emotional, and social functioning, along with disease-specific symptoms, financial impact, and global QOL. In addition to the CORE questionnaire, one may also administer modules related to tumor site, treatment approach, or a QOL domain. Aaronson *et al.*[141] reported acceptable to good reliability coefficients for individual scales (Cronbach's alpha = 0.65–0.92) and seven scales predict differences in patient clinical status.[141,142] It has been used in numerous studies with cancer survivors, including breast,[56,107,143,144] Hodgkin lymphoma,[145] colorectal,[97] prostate,[107,146–151] and lung.[152–159]

Functional Assessment of Cancer Therapy—General, Version 4 (FACT-G).[27] The FACT-G is a 27-item self-report measure of general questions divided into four primary HRQL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. The validation of this core measure in cancer and other chronic diseases has allowed for the evolution of multiple disease, treatment, condition, and non-cancer-specific subscales (over 40 different FACIT scales and 9 symptom indices), which are considered to be part of a larger measurement system called the Functional Assessment of Chronic Illness Therapy (FACIT). Each is intended to be as specific as necessary to capture the clinically-relevant problems associated with a given condition or symptom, yet general enough to allow for comparison across diseases, and extension, as appropriate, to other chronic medical conditions. The FACT-G and FACIT scales and indices have demonstrated adequate internal consistency (Cronbach's alpha = 0.56–0.89) and test–retest reliability (Pearson's $r = 0.92$), as well as evidence of validity (known groups, criterion, concurrent, and discriminant) and sensitivity to change.[22,27,34,143,160–164] It has been used in different cancer survivor studies, including oral cancer,[165] head and neck cancer,[166] breast cancer,[167] Hodgkin's disease,[168] hypogonadism,[93] and a study examining income disparities among survivors.[169]

Functional Living Index-Cancer (FLIC).[170] Also referred to as the Manitoba Functional Living Cancer Questionnaire, the FLIC is a 22-item measure that has been used extensively with people with cancer.[171–174] Using a linear analogue scale, respondents are provided with a 7-point Likert response scale that is superimposed on the rating line.[175] Item content deals with cancer-related symptoms and the extent to which they disrupt ones life.[176] A total score can be calculated, as well as five subscales (physical well-being, psychological well-being, hardship due to cancer, social well-being, and nausea), which have demonstrated satisfactory psychometric properties, including adequate internal consistency reliability (Cronbach's alpha = 0.78–0.83), validity (criterion and convergent), and sensitivity to change.[125,177–180] It has been used widely with cancer survivor populations, including breast,[7] prostate,[125,178] and lung cancer.[124,181]

Lerman Cancer Worry Scale (LCWS).[182] The LCWS is a 4-item scale developed to measure risk-related worry about developing cancer and the effect of worry on daily functioning. It has been used with cancer survivors[183] and has demonstrated adequate internal consistency in subsequent reports (Cronbach's alpha = 0.86).[184] Scores are calculated from 1 (no worry) to 4 (maximum worry).

Long Term Quality of Life Scale (LTQL).[185] The LTQL is a 46-item self-report measure designed to assess long-term QOL in female cancer survivors. Containing four subscales (Somatic Concerns, Philosophical/Spiritual View of Life, Health Habits, and Social/Emotional Support), items are rated on a 5-point scale (0 = low quality of life; 5 = high quality of life). Adequate reliability evidence has been reported (Cronbach's alpha = 0.86–0.89).[185–187]

Memorial Symptom Assessment Scale (MSAS).[188] The MSAS is a 32-item self-report scale that evaluates common cancer-related symptoms. Responses are rated according to severity, frequency, and extent of symptom-related distress. Three subscales are produced (Global Distress Index, Psychological Symptoms, and Physical Symptoms) which have demonstrated adequate internal consistency (Cronbach's alpha = 0.83–0.88) as well as convergent, discriminant and construct validity.[188]

Mental Adjustment to Cancer Scale (MAC).[189] The MAC is a 40-item self-report measure used to assess a person's ability to cope with cancer and treatment. It contains four subscales (fighting spirit, anxious preoccupation, hopeless/helplessness, and fatalism), with an additional item that deals with denial/avoidance. Respondents are asked to rate on a 4-point scale whether these coping strategies apply to them or not. Previous studies have reported sufficient reliability for subscales (Cronbach's alpha = 0.55–0.84), including construct, concurrent, and convergent validity.[190] It has been used with long-term cancer survivors.[55,60]

Quality of Life Index—Cancer Version III (QLI-CV III).[191] The QLI-CV III is a 66-item self-report scale that measures satisfaction and importance of different aspects of one's life. Providing a total score and four subscale scores (health and functioning, psychological/spiritual, social/economic, and family), respondents rate each item on a 6-point scale from 1 (very dissatisfied/very unimportant) to 6 (very satisfied/very important), with higher scores indicating higher satisfaction/importance.[191–195] Used in cancer survivor studies,[194,196] good psychometric properties have been reported across several studies. The QLI-III-CV has demonstrated good internal consistency (Cronbach's alpha) with breast cancer survivors for the total score (0.95) and subscales health and functioning (0.90), psychological/spiritual (0.84), social/economic (0.93), and family (0.66).[193] Content and construct validity have also been reported, as well as sensitivity to change.[191,197]

Quality of Life—Cancer Survivors (QOL-CS).[198] The QOL-CS is a 41-item self-report measurement tool designed to assess areas of concern among cancer survivors, including psychological well-being, physical well-being, social well-being, and spiritual well-being. Scores are rated on an 11-point scale (0 = worst outcome; 11 = best outcome) and subscale and total scores can be produced. The QOL-CS has demonstrated good test–retest reliability ($r = 0.88$–0.90 across subscales), internal consistency (Crobach's alpha = 0.71–0.93 across subscales) as well as content, predictive, concurrent, and construct validity.[103,161,198–200]

Quality of Life in Adult Cancer Survivors (QLACS).[201] The QLACS is a 47-item self-report scale that measures QOL issues important to cancer survivors. There are five cancer-specific domains (appearance concerns, financial problems, distress about recurrence, family-related distress, benefits of cancer) and seven generic domains (negative affect, positive affect, cognitive difficulty, sexual problems, pain, fatigue, and social withdrawal). Scores are rated on a 7-point scale (never = 1; always = 7). The QLACS has demonstrated good internal consistency (Cronbach's alpha ≥ 0.72 for each domain) as well as construct/and convergent validity.

Rotterdam Symptom Checklist (RSC).[202] The RSC is a 30-item self-report measurement tool designed to assess physical and psychological distress in cancer patients. Items are organized into three primary domains (physical symptoms, psychological symptoms, activities of daily living) and scores are rated on a 4-point scale (not at all to very much). Good subscale internal consistency evidence has been reported

(Cronbach's alpha = 0.82–0.95), as well as convergent validity evidence.[202] The RSC has been used extensively in studies with cancer patients.[202–206]

Sexual Activity Questionnaire (SAQ).[207] The SAQ is a 21-item measure that assesses sexual functioning in female cancer patients. Items are grouped into three content areas (hormonal status, reasons for sexual inactivity, and sexual functioning). Factor analysis yielded a three-factor structure of the sexual functioning domain: pleasure (desire, enjoyment, satisfaction), discomfort (vaginal dryness and dyspareunia), and habit (frequency of sexual behavior). Overall, the SAQ has good internal consistency (Cronbach's alpha = 0.66–0.71), test–retest reliability (0.68–1.00) as well as concurrent and construct validity.[207–210]

UCLA Prostate Cancer Index (UCLA PCI).[211] The UCLA PCI is a 20-item self-report measure for men receiving treatment for early-stage prostate cancer. The measure consists of six scales assessing functioning over the previous 4 weeks: urinary function, sexual function, bowel function, urinary bother, sexual bother, and bowel bother. Validated on a sample of long-term survivors of prostate cancer treatment, the UCLA PCI has internal consistency (Cronbach's alpha) reliability coefficients ranging from 0.65 to 0.93. and test–retest reliability of 0.92 (1 week).[212] Construct and convergent validity have also been reported.[211]

4.0. LONG-TERM CARE FOR CANCER SURVIVORS: INATTENTION TO ISSUES IMPACTING HRQL

Although health providers are taught measurement principles from the beginning of their clinical training (e.g., height, weight, vital signs), clinicians are not routinely taught how to measure patient-reported symptoms and health status across the cancer spectrum. Optimal cancer care throughout extended survivorship includes obtaining a complete picture of ones' physical and psychosocial health status; however, assessment and subsequent communication about these issues in medical consultations is often limited.[213–215] Oncology specialists may overlook symptoms due to training emphasis on cancer biology, productivity pressures, and a care reimbursement policy that offers incentives for procedures or drugs and disincentives for consultation time. Therefore, insufficient attention is paid to patient symptoms and HRQL concerns when making treatment or clinical management decisions.[213,215–219]

In 2005, the Centers for Medicare & Medicaid Services (CMS) conducted a 1-year demonstration project for cancer patients undergoing chemotherapy. CMS provided payment of $130 per encounter to clinics that reported data on patient-reported outcomes including pain, nausea and vomiting and fatigue. CMS has identified codes to provide reimbursement for supportive care. Extending this financial incentive into survivor care could significantly improve recognition and potential service delivery. Providing quality care, including symptom management, is highly valued by oncology providers.[149,219–221] The recent Institute of Medicine (IOM) report aims to raise awareness of the medical, function, and psychosocial consequences of cancer and cancer treatment and identify strategies for the provision of quality health care. The routine measurement of HRQL in clinical practice has the potential to improve health care for survivors by identifying areas most impacted by long-term sequelae of cancer and its treatment thus systematically identifying areas for intervention. The section below written by a cancer survivor illustrates some of the frustrations with inadequate long-term care and the potential benefits of systematic HRQL assessment throughout survivorship.

Box 1: A Cancer Survivor's Perspective

Patients have a difficult time discussing symptoms with their physicians. They may lack the language to explain what they are feeling and what the symptoms may signal to the patient—the individual's context. Many patients see every symptom as an indication their cancer has returned or worsened. This scares them, so they either deny the symptom or experience distress. Neither response leads to effective communication between and patient and their clinical team.

Patients are not always completely honest with their physicians. They want their physicians to see them as "good patients." Their concern is that bad patients will not get good care. Good patients don't complain. Good patients look healthy, as if they are responding to treatment. Some of my female friends, who had metastatic disease, told me they made sure they put on make-up and took extra care with how they looked when they went to see their physician so he/she would see them as worth saving. They wanted to be given the latest treatments. They didn't want their physicians to give up on them. Consequently, clinicians may underestimate the presence and severity of patients' symptoms.

For these reasons, patient-reported measurements of symptoms and health-related quality of life are crucial to good patient–physician communication and adequate health care for survivors. The act of systematically assessing the patient through self-report measures opens the lines of communication. Patient-reported measurements validate the importance of patients communicating their symptoms to their physicians and use patient experiences to be the source of data. This engages the patient in the process and makes them feel that they are part of the health care team not the objectified, disembodied malignant breast, colon or lung. It provides important information to the physician and may forestall a trip to the emergency room because of serious or life-threatening side effects of treatment or disease. It may prevent the development of a long-term side effect the individual may live with for 10 or 20 years after treatment.

Having a tool (i.e., self-report questionnaire) to allow the conversation about symptoms and health-related quality of life to be initiated between the patient and the physician makes the discussion about symptoms an integral part of the patient's treatment. Answering the questions through a patient-focused discussion of their quality of life makes the patient the center of the discussion. The discussion no longer is about "patients with your diagnosis or treatment" but about you and your symptoms and quality of life. Including social and emotional well-being in the patient/physician communication expands the conversation to a desire to make the patient whole, not just disease-free. It makes participating in the discussion part of being that "good patient."

5.0. INNOVATIVE APPROACHES TO HRQL MEASUREMENT

Clinical service delivery can be improved by refining the measurement of common symptoms and related HRQL, and connecting that measurement to clinical practice improvement efforts as well as the comprehensive study of multiple outcomes. The availability of multidimensional self-report HRQL instruments has allowed investigators to measure the impact of disease and its treatment on well-being and functioning. These instruments can capture important group differences or changes over time and better document the adverse and positive impact of disease, treatment side effects, and tumor response.[222–228] Their success over the last 15 years in articulating the impact of cancer and its treatments has led many to request the logical next step: measuring HRQL in individuals, tracking their progress over time, and using responses to inform care. Unfortunately, these compact multidimensional instruments are too coarse for individual assessment.[43,229–231] Their brevity, critical for inclusion in large-scale studies, is a major limitation in the individual assessment of cancer survivors. Error in individual assessment results is unacceptably wide. The confidence intervals for diagnostic and treatment decision-making purposes are too broad. The recent introduction of item response theory (IRT) and its application in computerized adaptive testing offer a solution by providing brief assessment precise enough for individual classification.[231–236] We [229,232,237–239] and others have shown that using computer adaptive testing with refined, well-defined banks of questions can select only those that provide the most health information and therefore increase precision.

5.1. Item Response Theory and Item Banks

Item response theory is a family of mathematical models used to determine the characteristics (difficulty) of test questions and to estimate the level of people on the underlying dimension being measured.[239–241] It posits an underlying, unobserved trait on which items are hierarchically arrayed. The three most popular unidimensional IRT models are the one-, two-, and three-parameter logistic models, based on the number of item parameters each incorporates.[242]

An item bank is comprised of carefully calibrated questions that develop, define, and quantify a common theme and thus provide an operational definition of a "trait." [238,243–249] A good bank covers the entire continuum of the latent trait being measured (Figure 2). The items in the bank are concrete manifestations of positions along the continuum that represent differing amounts of that trait. An HRQL item bank can provide a basis for designing the best possible set of questions for any particular application. A well-calibrated item bank makes it possible to compare the amount of a given trait for survivors who complete different sets of questions in the bank. Not only does this allow for tailored, "adaptive" testing, it also allows comparison across studies using different items from the same bank. Because all items are calibrated onto one common scale, one can compare HRQL results across diverse groups of survivors and item sets. A well-organized item bank with wide ranging item difficulties can also enable one to select items to construct a wide variety of tests, depending on the target populations and purpose of assessment. At a given difficulty level, any chosen item should provide the same increment of information. In the specific context of HRQL (or one of its dimensions), the content of questions at comparable difficulty levels may vary in clinical relevance. By using item bank information, the user is then able to select that item, within a given difficulty level, according to its clinical relevance. Specific items can thus be selected from among those in the bank to maximize precision of the estimate and clinical relevance of the questions. With computer adaptive tests, collaborative interaction between clinicians and programmers of the algorithm allows one to select the best set of items to obtain an estimate.

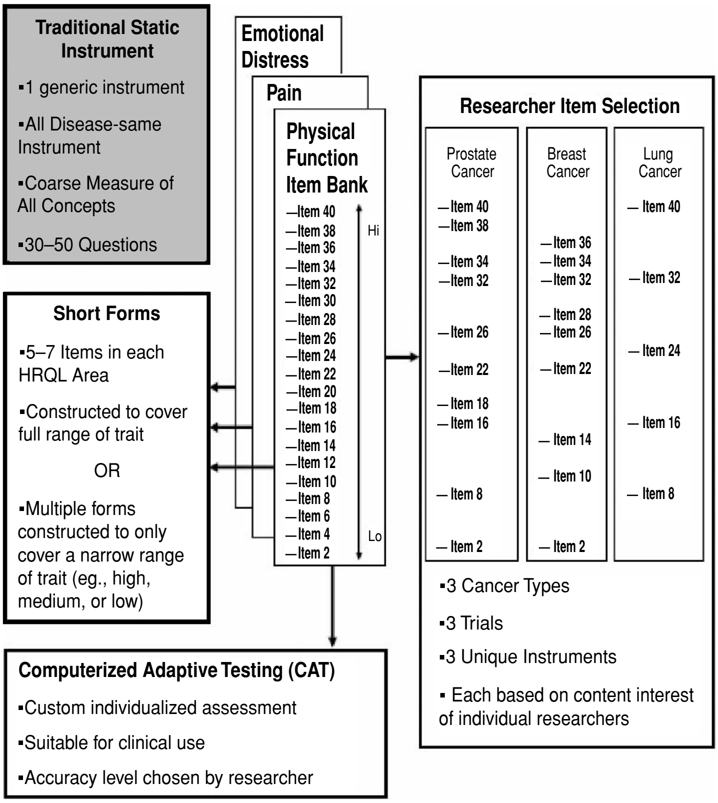


Figure 2. Calibrated Item Bank.

Figure 2 illustrates how three different researchers, studying three different types of cancer, can access the same generic item bank and select unique short forms of varying length and clinical content, and yet still produce a score for each person across the three trials that is on the same metric. An added feature is that, because the IRT measurement model uses logistic regression as its basis, this similar metric across the three short forms and clinical trials is on an interval scale. The interval scale nature of the metric comfortably allows for parametric statistics to be applied to trial data, offering more power in the statistical test, and perhaps having a beneficial effect on sample size requirements for trials in which the sample size is driven by the HRQL endpoint. Finally, also indicated in Figure 2, IRT item banks permit a degree of precision in assessing the individual person. Because they are replete with related items that are calibrated on a continuum of the concept being measured, IRT item banks are built for computerized adaptive testing, which selects the most informative questions from the bank until a sufficiently precise estimate of the person's score is obtained.

5.2. Computer Adaptive Testing

Computer adaptive testing is a method of administering tests by computer, based on the psychometric framework of IRT. Adaptive tests are greatly facilitated by a computer because of the computational requirements of the algorithm and the logistics of item and data management.[250,251] Items are selected on the basis of the examinee's responses to previously administered items.[239,252–254] This process uses an algorithm to estimate person "ability" and then chooses the best next item, enabling test administration based on specifications such as content coverage and test length. The capacity to rank all examinees on the same continuum, even if they have not been given any common items, allows for a test that is individually tailored to each examinee. With item banking, each patient need only answer a subset of items to obtain a measure that accurately estimates what would have been obtained by administering the entire set of items.

6.0. "REAL TIME" SYMPTOM MONITORING WITH CANCER SURVIVORS

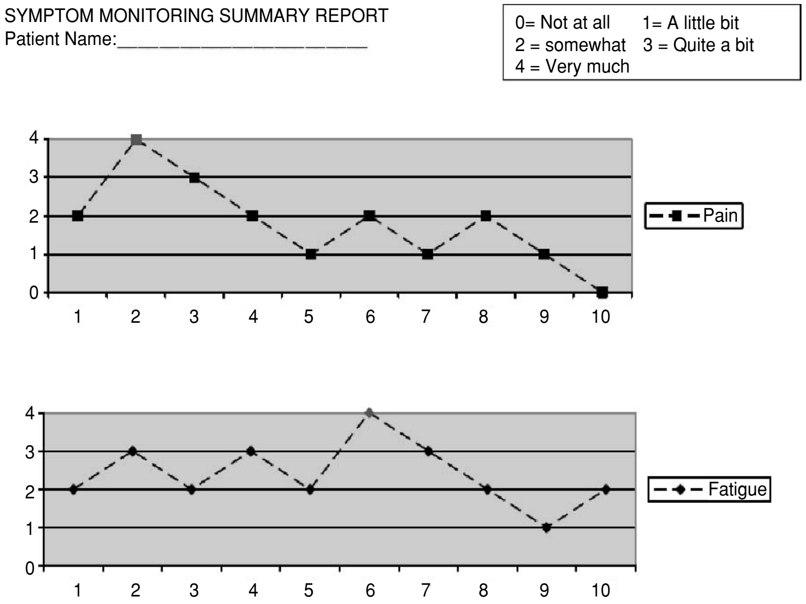
The use of computer adaptive tests with cancer survivors would minimize burden and help focus assessment. It has potential to sharpen measurement precision with a minimum number of questions[255] and has several unique advantages: (1) compared to paper-and-pencil tests, computer adaptive testing technology is efficient, requiring fewer questions to arrive at an accurate estimate; (2) it allows respondents and providers to receive immediate feedback on the person's HRQL status; (3) with its IRT underpinnings, it allows users to communicate with one another in a common language and metric; (4) the problem of excessive floor or ceiling effects is greatly reduced (yielding scores that promote accurate selection and classification decisions and reducing respondent boredom or frustration); and (5) since computer adaptive testing automates test administration, scoring and recording, human error is eliminated.

As a result, self-report information can be viewed differently from all other data used in clinical practice. Further, a growing evidence base suggests that routine, formal assessment of patient-reported symptoms and health status may improve communication between patient and physician,[213,256] satisfaction with care,[257,258] and HRQL.[259] Though studies are mixed, some research suggests benefit from routine assessment of HRQL in clinical practice including: (a) aiding detection of physical or psychosocial problems that otherwise might be overlooked, (b) monitoring disease and treatment, (c) allowing timely alterations in treatment, (d) facilitating patient–physician communication, and (e) improving the delivery of care.[260–269] There is a need for future research on the applicability and clinical utility (i.e., improving specific outcomes) of such an approach.

At present such practice is rare, especially during survivorship, in part because HRQL measures have diverse scaling properties and require a high degree of sophistication to understand and appropriately interpret. Other barriers to the integration of HRQL data into clinical practice include: (1) physician misunderstanding of HRQL, including the belief that it cannot be measured reliably; (2) physician tendency to disregard subjective patient data in favor of objective data; and (3) time, effort, and cost required to accomplish valid assessment.[149,216,270–273] For these reasons, results from these assessments need to be presented in an efficient user friendly format that includes reference or normative data.[274] In addition, results and interpretation of health status information must be delivered in a way that guides intervention.[259,275]

Quality of care and HRQL during survivorship may be improved by routine symptom and function monitoring used to trigger care management recommendations. Since computer adaptive testing enables brief-yet-precise measurement of clinically relevant symptoms and functional limitations in oncology practice, it can allow clinicians to monitor individual patients and detect small but important changes. Specific care recommendations can then be based on the level, or change in level, of a given symptom.

For example, completed and ongoing projects in our research lab utilize computer data processing and transaction services to telecommunication devices to collect weekly patient symptom and HRQL information. Patients with newly diagnosed or recurrent advanced lung cancer who are beginning any line chemotherapy telephone a computerized survey system weekly to complete a brief lung cancer-specific symptom index for 12 weeks, in addition to measures of HRQL and treatment satisfaction at baseline, 6 and 12 weeks. Results from a pilot trial support the use of computer and telephone technology as a means of collecting weekly data as well as the use of graphic reports as part of routine physician visits. A nurse monitors patient responses on the weekly symptom survey. The nurse contacts any patient who endorses any symptom severity as "very much" or "quite a bit" or reports a 2-point worsening from the previous week within 24 hours. The nurse verifies the accuracy of the report and either provides education or counseling (e.g., energy conservation, reminders on medication adherence) to the patient and/or calls the patient's physician for further consultation on symptom management (e.g., medication change, new diagnostic tests, office visit). In this way, the physician is engaged in active symptom management between clinic visits. Summary reports with graphic displays of cumulative symptom and HRQL information are generated (Figure 3), reviewed and discussed with patients at each physician visit, at which time patients also rate acceptability and satisfaction with



SYMPTOM MONITORING SUMMARY REPORT
Patient Name:______________________

0= Not at all 1= A little bit
2 = somewhat 3 = Quite a bit
4 = Very much

Figure 3. Symptom Monitoring Summary Report.

the system, and patients and physicians rate the utility and understandability of the report.

Similar symptom monitoring could be applied to cancer survivor medical follow-up appointments, since computer adaptive tests are scored in real-time and results could be presented in graphic and/or written reports immediately to the physician and patient, enabling a focused discussion status and options.[232,276] Patients have reported these discussions improve communication with providers[213,256] and may encourage better care.[277] This represents another area where improved surveillance may impact quality of care during survivorship and needs to be systematically investigated.

7.0. CONCLUSION AND FUTURE RESEARCH

There is a vast range of assessment options and methods of data capture available to researchers in cancer survivorship. Computer technology enables real-time monitoring in clinical practice using paper, telephone, PC-based or web-enabled assessment and evaluation. This pool of available technology can and should contribute to improving care for cancer patients during active treatment and into long-term survivorship. The reach of these opportunities will hopefully extend beyond oncology practice and back into primary care. Further research is needed to develop and test specific applications and their contribution to care. Active patient participation in care will likely benefit all.

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Part II

Common Problems

Chapter 7

Exercise Motivation and Behavior Change

Kerry S. Courneya, Kristina H. Karvinen, and Jeffrey K.H. Vallance

1.0. INTRODUCTION

Exercise motivation and behavior change is a major challenge in any population but it is especially problematic in chronic disease populations such as cancer survivors. Cancer survivors often endure long and difficult medical treatments that may make exercise participation more difficult and the potential benefits of exercise seem less relevant. Given the preliminary positive findings concerning the benefits of exercise in cancer survivors (see Chapter 7), research has begun to examine exercise motivation and behavior change issues in cancer survivors. In this chapter, we provide an overview of this topic. We begin by reviewing studies on the patterns and prevalence rates of exercise in cancer survivors both during and after medical treatments. We then review and summarize what we currently know about the determinants of exercise in cancer survivors. After that, we review the limited research on exercise behavior change interventions in cancer survivors. Finally, we discuss important future research directions for this field and the clinical and public health implications of this research.

2.0. EXERCISE PATTERNS AND PREVALENCE RATES IN CANCER SURVIVORS

The first important step in behavior change research is to establish the patterns and prevalence rates of the behavior for a given population of interest. Researchers have attempted to document the exercise patterns of cancer survivors using several different approaches. In one approach, cancer survivors are asked to retrospectively or prospectively report their exercise behavior at various time points (e.g., before diagnosis/treatments, during treatments, posttreatments) and then the researchers compute change scores among the different time periods.[1–4] In another approach, cancer survivors are directly asked if their exercise behavior has changed since their diagnosis/treatments.[5] In a third approach, cancer survivors are asked to report their exercise behavior at one point in time and their responses are then compared to matched controls without cancer or some other group of interest.[6]

In two of the earliest studies to quantify the exercise patterns of cancer survivors, Courneya and Friedenreich[1,2] surveyed 167 breast cancer survivors and 130 colorectal cancer survivors and asked them to retrospectively report their frequency of light, moderate, and vigorous intensity exercise before their diagnosis, during the time of their adjuvant treatments, and since the completion of their treatments. In both studies, participants reported significantly less moderate and vigorous exercise during their active treatments compared to their prediagnosis time period. Moreover, although participants in both studies reported more moderate and vigorous exercise in the posttreatment time period compared to the active treatment time period, it was still lower than that reported for the prediagnosis time period (Figures 1 and 2). The authors concluded that cancer treatments have a profound negative effect on the exercise behavior of cancer survivors that is not recovered even years after treatments are completed.

In perhaps the largest study to date, Irwin and colleagues[3] surveyed over 800 breast cancer survivors 4–12 months postdiagnosis about their physical activity levels in the year before their diagnosis and in the past month since their diagnosis. These researchers found that overall physical activity levels decreased by 2 hours or about 11% after diagnosis. In one of the early prospective studies on exercise patterns, Courneya and colleagues[7] followed 66 postsurgical colorectal cancer survivors from 2 to 6 months after their surgery. Results showed that study participants reported a significantly lower frequency of vigorous exercise compared to what they reported for the prediagnosis time period. No changes were reported in light or moderate exercise.

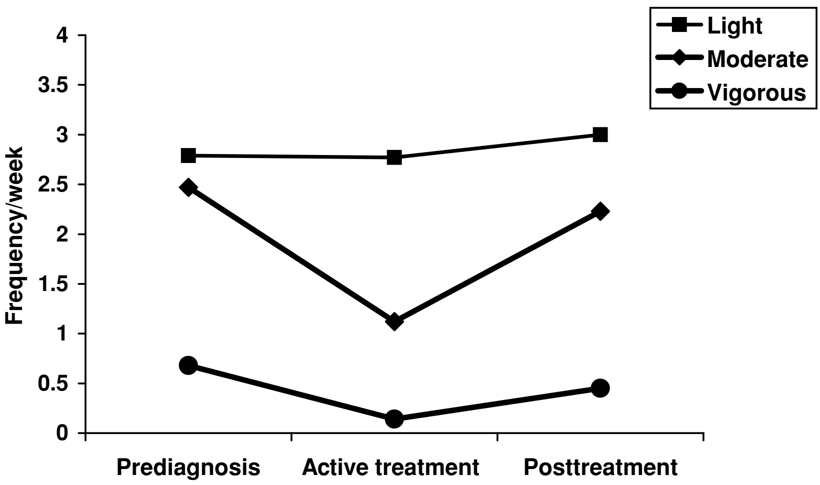

Figure 1. Changes in Exercise Frequency by Intensity Level Across the Breast Cancer Experience ($N = 167$). (Data are from Courneya and Friedenreich.[2])

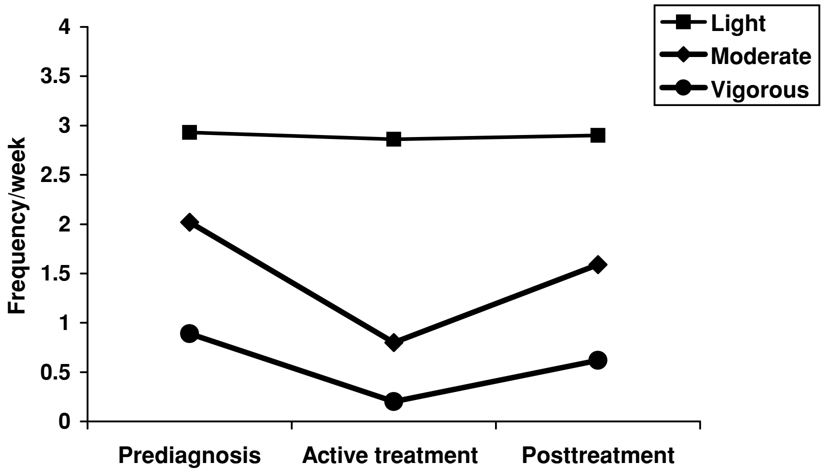

Figure 2. Changes in Exercise Frequency by Intensity Level Across the Colorectal Cancer Experience ($N = 130$). (Data are from Courneya and Friedenreich.[1])

Blanchard *et al.*[5] conducted an interview of 352 mixed cancer survivors (44% breast) attending one of four different outpatient clinics in the United States. Participants were asked during the interview if their exercise levels had changed since their diagnosis. Overall, 53% of participants said that their exercise levels had not changed since their diagnosis, 31% reported a decline in exercise levels, and 16% reported an increase (Figure 3). Moreover, of those not currently exercising regularly, 39% reported that their exercise levels had decreased since their diagnosis compared to just 6% reporting an increase. These data suggest that up to twice as many cancer survivors report a decrease, as opposed to an increase, in exercise levels after their diagnosis.

In terms of estimating the prevalence rates of exercise in cancer survivors, most recent research has adopted the public health guidelines recommended by the

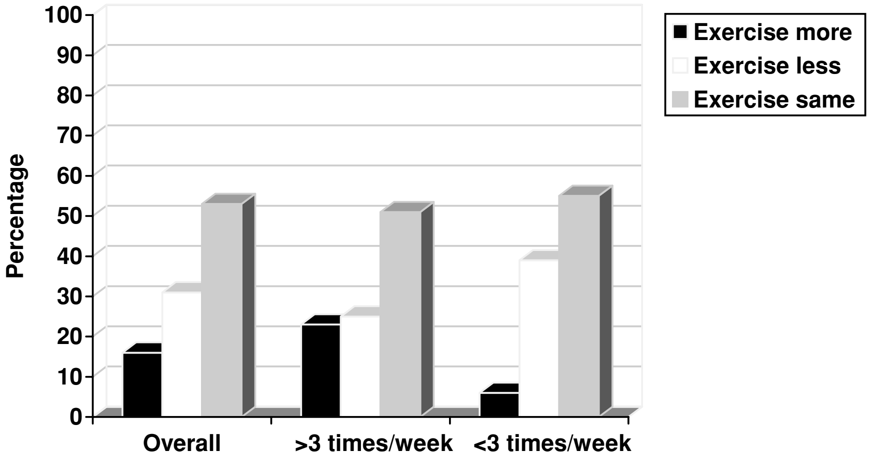

Figure 3. Changes in Exercise Behavior Since Diagnosis by Current Exercise Status in Mixed Cancer Survivors ($N = 352$). (Data are from Blanchard *et al.*[5])

United States Centers for Disease Control and Prevention and the American College of Sports Medicine.[8] These guidelines recommend that adults perform either 20–30 continuous minutes of vigorous exercise 3 days per week (e.g., jogging) or accumulate 30 or more minutes of moderate exercise 5 days per week (e.g., brisk walking). Although these guidelines are likely appropriate for cancer survivors who have completed their primary treatments and are considered disease-free, it is unclear if they are appropriate for cancer survivors currently receiving intensive treatments or having existing disease. Presently, there is no consensus on exercise guidelines for cancer survivors during various treatments.[9,10] In the absence of such guidelines, it seems reasonable to use the public health guidelines when estimating prevalence rates both during and after treatments.

In perhaps the most comprehensive prevalence study to date, Coups and Ostroff[11] reported data from the National Health Interview Survey conducted in 2000 with over 32,000 adults including over 1600 cancer survivors. The authors reported no differences in exercise participation rates between cancer survivors and non-cancer controls in the younger (18–39 years) and older (65+ years) cohorts but did report a significant difference in the middle-aged (i.e., 40–64 years) cohort (Figure 4). More specifically, approximately 31% of middle-aged non-cancer controls were physically active compared to just 25% of middle-aged cancer survivors. The low rate of exercise participation was consistent across cancer survivor subgroups and ranged between 20 and 30% (Figure 5).

Similar results have been reported by our group across a range of cancer survivors (e.g., non-Hodgkin's lymphoma, multiple myeloma, endometrial) using population-based provincial cancer registry data from Alberta, Canada.[12–14] In addition to asking about current exercise rates in these studies, Courneya and colleagues also asked survivors to retrospectively recall their exercise behavior during treatments. The results of these studies have shown that approximately 20–30% of cancer survivors report meeting public health exercise guidelines posttreatment but only 5–10% report meeting the guidelines during treatment (Figure 6).

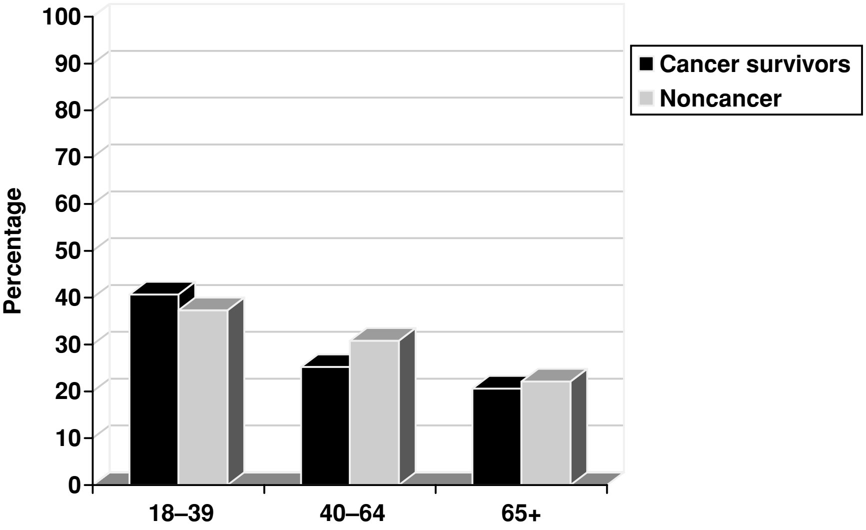

Figure 4. Percentage of Cancer Survivors ($N = 1646$) and Non-Cancer Controls ($N = 30,700$) Meeting Public Health Exercise Guidelines by Age Cohort. (Data are from Coups and Ostroff.[11])

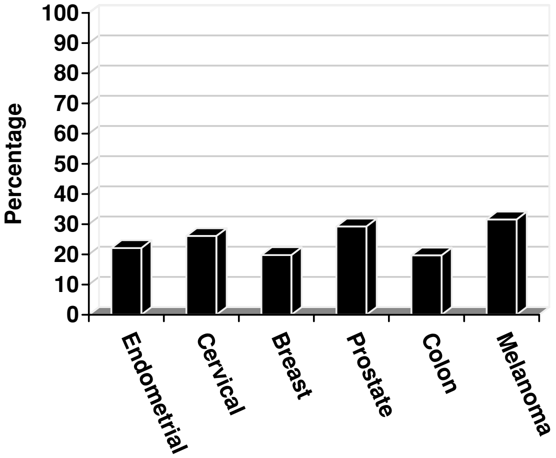

Figure 5. Percentage of Various Cancer Survivor Groups ($N = 1250$) Meeting Public Health Exercise Guidelines. (Data are from Coups and Ostroff.[11])

In one of the few studies using the Transtheoretical Model's[15] stages of change construct to describe exercise patterns and prevalence rates in cancer survivors, Rhodes, Courneya, and Bobick[16] surveyed 175 breast cancer survivors and asked them to report their current stage of change as well as to recall their stage of change during treatment. In recalling the active treatment period, 24% of breast cancer survivors reported being in the precontemplation stage (i.e., they did not exercise and did not even think about exercising), 10% in the contemplation stage (i.e., they did not exercise but they did think about exercising), 47% in the preparation stage

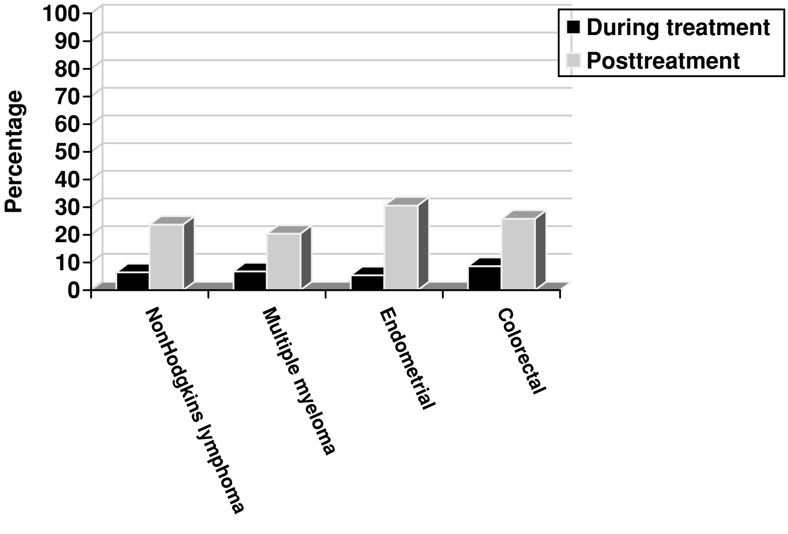

Figure 6. Percentage of Various Cancer Survivor Groups ($N = 1310$) Meeting Public Health Exercise Guidelines. (Data are from Vallance *et al.*[14]; Jones *et al.*[13]; Courneya *et al.*[12]; Peddle, C.J. (2005). *Exercise motivation in colorectal cancer survivors: An application of self-determination theory.* Unpublished Master's Thesis, Faculty of Physical Education, University of Alberta, Edmonton, AB, Canada.)

(i.e., they exercised some but not regularly), and only 19% in the action or maintenance stages (i.e., they exercised regularly). In terms of their current exercise stage of change, 5% reported being in precontemplation, 12% in contemplation, 41% in preparation, and 42% in action or maintenance. These data indicate that about a quarter of all breast cancer survivors report not even thinking about exercising during their treatments.

Other studies have also examined cancer survivors' readiness to change their exercise behavior after a diagnosis. For example, Jones and Courneya[17] reported that 84% of cancer survivors preferred to receive exercise counseling at some point during their cancer experience. Similarly, Vallance *et al.*[14] reported that 77% of non-Hodgkin's lymphoma (NHL) survivors were receptive to receiving exercise counseling at some point after their NHL diagnosis. In a larger sample of breast and prostate cancer survivors, Demark-Wahnefried *et al.*[18] reported that 80% were interested in receiving health promotion programs during their cancer experience. Furthermore, 51% indicated a specific interest in receiving exercise programs.

Overall, the data on exercise patterns and prevalence rates suggest that cancer survivors experience a significant decrease in their exercise levels during active treatments. There is some natural recovery of exercise levels after treatments but they do not usually return to prediagnosis levels. Moreover, the actual exercise prevalence rates for posttreatment cancer survivors seems to range from 20 to 30% across a wide range of cancer survivor groups. These prevalence rates appear to be below that reported for matched controls and the general population. The actual prevalence rates of exercise for cancer survivors receiving treatments appear to be much lower, ranging from 5 to 10% across a wide range of cancer survivor groups. These prevalence rates are definitely below that reported for the general population.

Despite the consistencies in these data, there are important limitations in the research on exercise patterns and prevalence rates in cancer survivors. Perhaps the most important limitation is that all studies to date have relied on self-report data. It is well-known that self-report overestimates the exercise levels in most populations, consequently, it is likely that the prevalence rates presented here are higher than the actual rates. Second, many of the studies are transparent in nature, likely resulting in selection biases, which may also lead to overestimates of the exercise rates in the various cancer survivor populations. Third, many of the studies are retrospective which can create problems of memory and recall bias. Fourth, few studies are of a nationally representative sample and few have made comparisons to appropriately matched controls. Finally, it is not clear what the exercise guidelines are for cancer survivors, especially during treatments, and these guidelines may vary by cancer survivor group, symptoms, and prognosis.

3.0. DETERMINANTS OF EXERCISE IN CANCER SURVIVORS

Given the low exercise participation rates in many cancer survivor groups both during and after treatments, researchers have turned their attention to understanding the determinants of exercise in cancer survivors. Most early research was descriptive and atheoretical, selecting various demographic, medical, and psychosocial constructs to test as correlates and predictors of exercise behavior. Most recent research has applied one of the currently validated social cognitive models of human motivation and behavior to facilitate understanding. The two models that have been applied most often to exercise in cancer survivors have been the theory of planned behavior[19] and social cognitive theory.[20]

3.1. Social Cognitive Models Applied to Exercise in Cancer Survivors

Bandura's social cognitive theory (SCT)[20] is based on the concept of reciprocal determinism among behavior, the person, and the environment. Self-efficacy is considered the key organizing construct within SCT and is defined as "beliefs in one's capabilities to organize and execute the courses of action required to produce given levels of attainment" (p. 300).[21] Self-efficacy is theorized to influence the activities that individuals choose to approach, the effort expended on such activities, and the degree of persistence in the face of failure or obstacles.[22]

Another important construct in SCT is outcome expectation, which refers to the expected outcomes associated with the performance of a behavior. Outcome expectations serve as incentives or disincentives depending on whether the anticipated outcomes are positive or negative. Bandura[21] describes three main categories of outcome expectations labeled physical, social, and self-evaluative. Physical outcome expectations include the physical effects of a behavior such as pain, injury, and disease risk. Social outcomes include anticipated social reactions toward the behavior such as disapproval. Self-evaluative outcome expectations focus on one's own reaction to performing a given behavior (e.g., guilty, proud, embarrassed).

Ajzen's theory of planned behavior (TPB)[19] proposes that a person's intention is the immediate determinant of a behavior because it reflects a conscious decision to perform or not perform the behavior. Intention is hypothesized to be determined by attitude, subjective norm, and perceived behavioral control (PBC). Perceived behavioral control is the perceived ease or difficulty of performing the behavior and may directly predict the behavior if it is an accurate reflection of the person's actual control over the behavior. Attitude is a positive or negative evaluation of performing the behavior that includes both instrumental (e.g., harmful/beneficial, useless/useful) and affective (unenjoyable/enjoyable, boring/fun) components. Subjective norm reflects the perceived social pressure that individuals feel to perform or not perform the behavior and includes both injunctive (what others think) and descriptive (what others do) component. The primary propositions of the TPB are: (a) people will perform a behavior when they are motivated to do so and have the opportunity to do so and (b) people will be motivated to perform a behavior when they evaluate it positively, believe it will be enjoyable, perceive that others approve and also perform the behavior, and believe that the behavior is under their control and that they are capable of performing it.

The TPB also proposes that attitude, subjective norm, and PBC are comprised of underlying accessible beliefs in an expectancy-value formulation.[19] Attitude is a function of *behavioral* beliefs, which refer to the perceived advantages and disadvantages of performing the behavior. Subjective norm is a function of *normative* beliefs, which focus on the specific individuals or groups important to the individual who may or may not approve of the behavior. Finally, *control* beliefs underlie PBC and represent the opportunities and resources available to the individual for performing the behavior and their ability to influence the behavior.

3.2. Literature Review of Exercise Determinants in Cancer Survivors

Seventeen studies to date have examined social cognitive determinants of exercise in cancer survivors using a validated theoretical model (Table 1). Fourteen (82%)

Table 1. Summary of Theoretical Studies Examining Social Cognitive Determinants of Exercise in Cancer Survivors

Authors	Sample	Design	Results
Theory of Planned Behavior			
Courneya and Friedenreich[28]	110 colorectal cancer survivors receiving treatment	Retrospective	Intention and perceived behavioral control (PBC) were independent correlates of behavior ($R^2 = 0.22$) and attitude was an independent correlate of intention ($R^2 = 0.31$).
Courneya and Friedenreich[29]	164 breast cancer survivors receiving treatment	Retrospective	Intention and PBC were independent correlates of behavior ($R^2 = 0.14$) and attitude and subjective norm were independent correlates of intention ($R^2 = 0.23$).
Courneya *et al.*[7]	66 colorectal cancer survivors with 73% receiving treatment	Prospective	Intention was an independent predictor of behavior ($R^2 = 0.30$) and attitude was an independent correlate of intention ($R^2 = 0.23$).
Courneya *et al.*[40]	37 mixed cancer survivors receiving high-dose treatment	Prospective	Intention was an independent predictor of behavior ($R^2 = 0.14$) and attitude and PBC were independent correlates of intention ($R^2 = 0.68$).
Courneya *et al.*[25]	24 posttreatment breast cancer survivors training for dragon boat racing	Prospective	Intention was an independent predictor of behavior ($R^2 = 0.35$) and subjective norm was an independent correlate of intention ($R^2 = 0.49$).
Blanchard *et al.*[41]	83 posttreatment breast cancer survivors and 46 posttreatment prostate cancer survivors	Cross-sectional	In breast cancer survivors, intention was an independent correlate of behavior ($R^2 = 0.32$) and attitude and PBC were independent correlates of intention ($R^2 = 0.45$). In prostate cancer survivors, intention was an independent correlate of behavior ($R^2 = 0.37$) and PBC was an independent correlate of intention ($R^2 = 0.36$).
Courneya *et al.*[42]	51 mixed cancer survivors randomized to a 10-week home-based exercise program	Prospective as part of an RCT	Independent predictors of exercise adherence were sex (male), extraversion, normative beliefs (-), and PBC ($R^2 = 0.42$).
Rhodes and Courneya[43]	272 posttreatment mixed cancer survivors	Cross-sectional	Intention and PBC were independent correlates of behavior ($R^2 = 0.34$) and affective attitude, subjective norm, and PBC were independent correlates of intention ($R^2 = 0.46$).
Courneya *et al.*[44]	62 colorectal cancer survivors randomized to a 16-week home-based exercise program	Prospective as part of an RCT	Independent predictors of exercise adherence were exercise stage of change, employment status, treatment protocol, and PBC ($R^2 = 0.40$).
Courneya *et al.*[45]	82 prostate cancer survivors randomized to a 12-week supervised exercise program	Prospective as part of an RCT	Independent predictors of exercise adherence were exercise stage of change, age (-), and intention ($R^2 = 0.20$).

Courneya *et al.*[31]	399 posttreatment non-Hodgkins lymphoma survivors	Cross-sectional	Affective attitude, subjective norm, and PBC were independent correlates of intention ($R^2 = 0.55$).
Jones *et al.*[46]	70 posttreatment multiple myeloma survivors	Cross-sectional	Affective attitude, instrumental attitude, and PBC were independent correlates of intention ($R^2 = 0.43$).
Karvinen *et al.*[26]	354 posttreatment endometrial cancer survivors	Cross-sectional	Intention was an independent correlate of behavior ($R^2 = 0.24$) and affective attitude and self-efficacy were independent correlates of intention ($R^2 = 0.38$).
Keats *et al.*[47]	118 adolescent cancer survivors	Cross-sectional	Intention and self-efficacy were independent correlates of behavior ($R^2 = 0.29$) and affective attitude and instrumental attitude were independent correlates of intention ($R^2 = 0.34$).
Social Cognitive Theory			
Rogers *et al.*[23]	21 breast cancer survivors undergoing treatment	Cross-sectional	Higher average of steps per day was significantly associated with having a breast cancer exercise role model ($r = 0.56$) and higher annual income ($r = 0.61$). Higher daily energy expenditure was significantly associated with higher barrier self-efficacy ($r = 0.62$), higher task self-efficacy ($r = 0.77$), having an exercise partner ($r = 0.71$), and having a breast cancer exercise role model ($r = 0.74$).
Five Factor Model			
Rhodes *et al.*[43]	175 non-metastatic breast cancer survivors	Retrospective	During cancer treatment, contemplators were significantly higher in neuroticism than those in action/maintenance and preparers were significantly higher in extraversion than contemplators. At posttreatment, neuroticism was lower for those in action/maintenance compared to contemplators and preparers, extraversion and conscientiousness were significantly higher for those in the action/maintenance stage compared to those in contemplation and preparation.
Attribution Theory			
Courneya *et al.*[24]	46 mixed cancer survivors at the 5-week follow-up who had participated in the exercise arm of a 10-week long randomized controlled trial	Prospective	Perceived success and program exercise frequency were independent predictors of postprogram exercise frequency ($R^2 = 0.46$). Program exercise minutes was an independent predictor of postprogram minutes.

of these studies tested Ajzen's TPB.[19] Of these studies, two used a retrospective design, six used a cross-sectional design, three used a prospective observational design, and three were prospective as part of a randomized controlled trial. Three studies examined colorectal cancer survivors, three examined breast cancer survivors, three involved mixed cancer survivors, and two focused on prostate cancer survivors. Single studies have examined NHL survivors, multiple myeloma survivors, adolescent cancer survivors, and endometrial cancer survivors. Results indicated that between 14 and 37% of the variance in exercise behavior was accounted for by intention and PBC, and between 23 and 68% of the variability in exercise intention was influenced by attitude, subjective norm, and PBC. All studies found support for the TPB as a theoretical framework for understanding exercise behavior in cancer survivors, however, the constructs that made the most important contributions to predicting exercise behavior and intention varied by cancer survivor group.

Three studies to date have used other models as a theoretical basis for understanding correlates of exercise motivation in cancer survivors. One study used SCT,[23] one used attribution theory,[24] and one used the Five Factor Model of Personality.[16] Two studies involved breast cancer survivors and one examined mixed cancer survivors. Results suggested several important correlates of exercise participation including self-efficacy, the influence of others, personality, and perceived success.

One of the early prospective studies examined predictors of exercise behavior in 66 postsurgical colorectal cancer survivors.[7] Participants completed a baseline questionnaire that assessed the TPB, demographic and medical variables, and prediagnosis exercise. Exercise was monitored over a 4-month period by self-report and reported monthly by telephone. Hierarchical regression procedures indicated that intention and prediagnosis exercise were the key predictors of exercise behavior, and that attitude was the most important determinant of exercise intention. The authors concluded that the TPB was a useful framework for understanding determinants of exercise in this sample.

One of the first studies to examine predictors of an objective measure of exercise adherence focused on 24 breast cancer survivors attending a twice weekly 12-week training program for dragon boat racing.[25] At baseline, participants completed a questionnaire that assessed TPB constructs, past exercise, and demographic and medical variables. Exercise adherence was measured using objective attendance records. Multiple regression analyses indicated that intention was the key determinant of adherence to the exercise program, and that subjective norm was the sole independent determinant of intention. The authors concluded that the TPB may be an effective framework for use in the design of exercise interventions for breast cancer survivors.

One of the largest studies to date was a cross-sectional study of 354 endometrial cancer survivors.[26] Participants in this study completed a questionnaire that assessed the TPB, exercise participation, and demographic and medical variables. Multiple regression analyses indicated that intention was the sole independent correlate of exercise behavior, and self-efficacy and affective attitude were the key correlates of intention. Age was found to interact with intention and perceived control in the behavioral analyses. Intention was positively associated with behavior only in survivors under the age of 70 years, and perceived control was only associated with behavior in survivors over the age of 70 years. Additionally, BMI was found to interact with instrumental attitude and self-efficacy in the intention analysis. Instrumental attitude was positively associated with intention only in normal weight survivors, while self-efficacy was only associated with intention in obese survivors. The authors concluded that the TPB may be a useful framework for understanding correlates of exercise motivation and behavior in endometrial cancer survivors.

3.3. Exercise Motives and Barriers in Cancer Survivors

Early research into the specific exercise motives and barriers of cancer survivors reported that some exercise motives and barriers were unique to the cancer experience while others were common to other populations.[27–30] For example, Courneya and Friedenreich[28,29] asked breast and colorectal cancer survivors to recall the major benefits and barriers to exercise during their treatments. The main benefits of exercise that were reported were: (a) get mind off cancer and treatment, (b) feel better and improve well-being, (c) maintain a normal lifestyle, (d) cope with the stress of cancer and treatment, (e) gain control over cancer and life, (f) recover from surgery and treatment, and (g) control weight. The main exercise barriers in this group were: (a) nausea, (b) fatigue/tiredness, (c) no time to exercise, (d) no support for exercise, (e) pain or soreness, (f) no counseling for exercise, and (g) working at a regular job. These results indicate many unique exercise motives and barriers that are based on the cancer experience.

More recent research has examined larger and less-studied groups of cancer survivors.[26,31] For example, Courneya and colleagues[31] surveyed 399 NHL survivors. Participants were asked to list what they believed were the main advantages of exercise after their cancer diagnosis and the main factors that made it easier or more difficult for them to exercise during their cancer care. The seven most common perceived advantages of exercise were that it leads to: (a) a positive mental attitude, (b) muscular strength and tone, (c) aerobic fitness/endurance, (d) a sense of well-being, (e) increased energy, (f) improved circulation, and (g) stress relief. The seven most common perceived barriers to exercise were: (a) a lack of energy/fatigue, (b) being too deconditioned/too weak, (c) nausea, (d) pain, (e) feeling ill, (f) a lack of motivation/laziness, and (g) depression. The finding that deconditioning/weakness was the second most commonly identified barrier in NHL survivors is consistent with clinical observations of this population.

Similarly, Karvinen *et al.*[26] surveyed 354 endometrial cancer survivors. Participants were asked to list: (1) "...the main advantages of participating in regular exercise" (motives) and (2) the factors that "...make it difficult for you to exercise regularly" (barriers). The most common motives were: (a) lose weight, (b) feel better about one's self, (c) keep in shape, (d) improve strength/tone muscles, and (e) improve cardiovascular health. The five most frequently reported barriers were: (a) poor health, (b) lack of time, (c) poor weather conditions, (d) injury, and (e) fatigue/lack of energy. The finding that weight loss is the most commonly reported benefit of exercise is consistent with the obesity rate in this population.

Courneya, Jones, Mackey, and Fairey[32] examined the motives and barriers of 52 breast cancer survivors prior to participating in a randomized controlled trial. Over 90% of participants felt that it was quite or extremely likely that exercise would improve their energy level and their well-being, 70–80% felt that it would reduce their stress and improve their immune function, and 40–45% felt that it would reduce their risk of a recurrence and help them maintain a normal lifestyle. In terms of overcoming barriers, over 75% were quite or extremely confident they could exercise if the weather was bad, they had limited time, or they became tired or fatigued. They were less confident, however, that they could exercise if they experienced pain or additional family responsibilities and especially if they experienced a recurrence of their cancer or other medical/health problems.

In the only prospective study to date, Courneya and colleagues[33] examined the barriers to weekly exercise in 69 colorectal cancer survivors. In the trial, participants randomized to the exercise group were asked to report their exercise on a weekly basis by telephone. Those participants not achieving the minimum weekly exercise prescription (i.e., 3 times/week for 30 minutes) were asked for a primary exercise barrier. The most common barriers to exercise reported in this sample were lack of time/too busy (reported 65 times by 22 different participants), nonspecific treatment side effects (reported 51 times by 17 different participants), and fatigue (reported 44 times by 16 different participants). These three barriers accounted for 45% of all missed exercise weeks. The top seven barriers (including surgical complications, work responsibilities, progressing toward the exercise prescription, and getting enough activity elsewhere) accounted for 70% of all missed weeks and the top 10 barriers (including diarrhea, the flu, and nausea) accounted for almost 80% of all missed exercise weeks.

Overall, these studies indicate that cancer survivors have diverse motives and barriers to exercise, some of which are unique to the cancer experience and some of which are common to other populations. Not surprisingly, motives and barriers vary by treatment status. Barriers to exercise during treatment often reflect the well-known side effects of treatments (e.g., nausea, diarrhea, fatigue, depression) whereas barriers to exercise after treatments tend to realign with barriers in the general population (e.g., lack of time, too busy). It is also apparent that exercise motives and barriers vary by cancer survivor group reflecting the unique profile of the particular disease. For example, weight loss is the most common exercise motive in endometrial cancer survivors and deconditioning is a major exercise barrier in NHL survivors.

3.4. Exercise Preferences in Cancer Survivors

Although a number of studies have successfully explored social cognitive correlates of exercise motivation, relatively little is known about the exercise programming and counseling preferences of cancer survivors—factors that would also presumably influence exercise participation. Four studies to date have examined exercise preferences in cancer survivors.[17,34–36]

Vallance *et al.*[35] found, in a cross-sectional survey of 431 NHL survivors, that the majority of participants indicated that they were interested (81%) and able (85%) to participate in an exercise program for NHL survivors. Participants most commonly reported walking as the activity of choice (55%) and moderate level exercise as the preferred intensity (62%). More than half of participants (56%) indicated they would have preferred to start an exercise program at least 3 months after treatment. Equal proportions of participants indicated that they preferred to exercise alone (31%) or with others (35%).

Another cross-sectional study involving 386 endometrial cancer survivors reported similar findings.[36] In this study, the majority of participants also indicated that they would have preferred exercise counseling at some point after their diagnosis (75.7%) and felt able (81.7%) and interested (76.9%) in doing an exercise program. Participants also indicated that walking was the most commonly preferred activity (76.9%), most preferred moderate intensity exercise (61.1%), the most common preference for initiation of an exercise program was 3–6 months posttreatment

(39.3%), and participants were equally distributed among the desire to exercise alone (23.8%), with others (22.6%), or no preference (23.8%).

In an earlier cross-sectional study of 307 breast, prostate, lung, and colorectal cancer survivors, Jones and Courneya[17] found that the majority of participants (84%) would have, or possibly would have, been interested in exercise counseling at some point after diagnosis, preferred face-to-face exercise counseling (85%), and to receive counseling from an exercise specialist affiliated with a cancer center (77%). Walking was the preferred modality (81%), almost all preferred recreational activities (98%), half indicated a preference for moderate intensity exercise (56%), and before treatment was the time period most selected for the initiation of an exercise program (32%). The results of these studies suggest that cancer survivors may be interested in receiving exercise counseling and programming services; however, individual variation in the types of activities, intensity, partners, and structure do exist and need to be considered.

4.0. EXERCISE BEHAVIOR CHANGE INTERVENTIONS IN CANCER SURVIVORS

At present, few published studies have examined the effects of an exercise behavior change intervention in cancer survivors. Jones and colleagues[37] examined the effects of two oncologist-centered interventions on self-reported exercise behavior in breast cancer survivors beginning treatment. During their initial treatment consultation, participants were randomized to receive either: (a) an oncologist's recommendation to exercise, (b) an oncologist's recommendation to exercise plus a referral to a Kinesiologist, and (c) usual care (i.e., no recommendation). Results of this study indicated that participants receiving an exercise recommendation reported more exercise than those receiving usual care. The authors noted, however, that the initial treatment consultation may not be the opportune time to recommend exercise given the amount of information dispensed during this time and the stress level of the cancer survivor. Nonetheless, this trial suggests that advocating exercise behavior via an oncologist's recommendation may be an easy and efficient form of promoting exercise in cancer survivors.

Recognizing the need for efficient and effective methods that have the capacity to positively affect exercise behaviors, Demark-Wahnefried and colleagues have recently published two design papers that outline and describe two ongoing randomized controlled trials designed to test whether various health behavior counseling methods affect exercise behavior and fruit and vegetable consumption in breast and prostate cancer survivors. Project LEAD (Project Leading the Way in Education Against Disease)[38] is the first trial to test whether a 6-month personally tailored telephone-counseling program is effective in improving diet and exercise behaviors in early stage breast and prostate cancer survivors. Survivors are being randomized to an experimental or control group. The experimental group receives a mailed workbook and telephone counseling (tailored on stage of readiness) pertaining to overall diet and exercise behaviors. The control group receives a mailed workbook and telephone counseling in other health-related areas. The primary outcome of the study is physical function. Secondary outcomes include diet quality, exercise, body mass index, depression, quality of life (QoL), and perceived health.

FRESH START (a randomized trial of activity and diet among cancer survivors)[39] is designed to evaluate the efficacy and effectiveness of personally tailored print materials in promoting lifestyle changes in breast and prostate cancer survivors. Survivors in the intervention group receive the FRESH START intervention program that consists of a series of workbooks, newsletters, and update cards that are tailored based upon information collected during a baseline interview. Survivors in the control group receive non-tailored, health-promotion print materials that promote exercise and a healthy diet. Primary endpoints are exercise behavior and dietary intake. Secondary endpoints include perceived health, QoL, depression, and weight status. These aforementioned studies will provide important information pertaining to the efficacy of distance medicine-based approaches in promoting exercise in cancer survivors.

At the University of Alberta, we have recently developed a 62-page exercise guidebook for breast cancer survivors (*Exercise for health: An exercise guide for breast cancer survivors*) based on the theoretical components of the TPB. The information in the exercise guidebook was formulated and written based on behavioral, normative, and control beliefs elicited from breast cancer survivors in previous research. The guidebook consists of 10 chapters and includes participant-centered activities designed to enhance attitude (i.e., instrumental and affective attitudes), subjective norm (i.e., injunctive and descriptive norms), PBC (i.e., self-efficacy and controllability), and implementation intentions (e.g., goal-setting, planning). These written activities are also designed to facilitate participant engagement in the information. The exercise guidebook also incorporated previous research examining exercise preferences of breast cancer survivors.[2,32]

By examining potentially feasible, practical, and novel forms of exercise promotion in the cancer population, cancer care professionals (e.g., oncologists, nurses, physiotherapists, dieticians) can become aware of these approaches of communicating and promoting exercise information and behavior as an effective tool for assisting in exercise adoption and maintenance and further enhancing QoL after treatment(s) for cancer. These interventions may also offer the researcher a viable opportunity to reach, target, and influence a large number of individuals that otherwise would not be able to participate in clinically-based programs.

5.0. FUTURE RESEARCH DIRECTIONS

Research into exercise motivation and behavior change in cancer survivors is just beginning and we still need answers to many basic questions. In terms of descriptive behavioral epidemiology, we need more studies documenting the exercise patterns and prevalence rates of cancer survivors including the type, frequency, duration, and intensity of the activities. In particular, we need research on resistance exercise which has largely been neglected in public health and exercise oncology circles but is gaining support as a critical component of exercise for health and function, especially for middle-aged and older adults. Moreover, it may be useful to examine the patterns and prevalence rates of fitness parameters (e.g., aerobic capacity, muscular strength, function) as one source of objective information about the exercise behavior of cancer survivors. These research studies would benefit from using prospective designs and objective measures of exercise and/or fitness to improve the quality and validity of the data. The data will need to be collected in all cancer survivor groups including understudied groups (e.g., ovarian, bladder, lung). Data will also be needed for all the various cancer-related time periods (e.g., pretreatment, on various treatments, posttreatment, long term survivors). Ideally, these data will be population-based and should be compared to data from the general population and/or to data from other chronic disease populations (e.g., diabetes, heart disease). When these studies are completed, we will have a better understanding of the natural history of exercise behavior as modified by the cancer experience.

In terms of exercise determinants research, we need a greater appreciation of the factors that influence the various components of exercise behavior (e.g., type, intensity). As one example, we need research on the determinants of walking for exercise because walking is the most popular form of exercise for cancer survivors.[17] In terms of the determinants themselves, we need much more research on the broader range of determinants outlined in social ecological frameworks. These determinants may include non-modifiable demographic factors, disease factors (e.g., stage), medical factors (e.g., treatments, side effects), as well as modifiable variables such as elements in the physical and social environments, system factors (e.g., cancer care delivery), personality, and social cognitive variables. In terms of social cognitive variables, there is good evidence that the TPB is a useful framework for understanding exercise in cancer survivors but there are other validated theories that should also be tested (e.g., SCT, the transtheoretical model, self-determination theory). Similar to research on patterns and prevalence rates, we need determinants research that uses prospective designs and objective measures across the entire cancer experience in all cancer survivor groups. When these studies are completed, we will have a better understanding of how the determinants of exercise behavior are modified by the cancer experience.

In terms of exercise behavior change research, which by definition is intervention research, we need to apply rigorous randomized controlled trial methodology. Well-designed and properly executed randomized controlled trials will provide the best evidence of the effectiveness of exercise behavior change interventions in cancer survivors. Some of the key features of this methodology include a defined population, an appropriately powered sample size, proper randomization, blinding of assessors, balanced groups at baseline, an appropriate comparison group, fidelity to the intervention protocols, limited attrition, intention-to-treat analysis, and well-validated outcome measures. If well-conducted, large scale, multicenter trials demonstrate the effectiveness of an exercise behavior change intervention in cancer survivors, then public health organizations, cancer societies, cancer centers, cancer support groups, and cancer care professionals (e.g., oncologists, nurses, physiotherapists, nutritionists, clinical psychologists) will be more likely to adopt and disseminate these interventions.

Importantly, exercise behavior change research in cancer survivors should be informed by the exercise determinants research. Given that exercise determinants research should be guided by theory, this means that exercise behavior change interventions should also be guided by theory. Beyond the utility of a theory for the development of a behavior change intervention, the assessment of a theoretical model during an intervention also allows the determination of why a particular behavior change intervention either worked or did not work for a given cancer survivor group in a given context. This information can then be used in further refinement of the intervention.

Similar to research on the prevalence and determinants of exercise, there will be a strong need to develop behavior change interventions that can motivate and facilitate exercise participation in various cancer survivor groups (e.g., breast, prostate) at all phases of the cancer experience and across clinical settings (e.g., during intensive in-patient and out-patient treatments) and population-based or public health settings (e.g., long term survivors, rural survivors). The nature and content of these behavior change interventions may vary based on all the factors mentioned earlier and should include multilevel interventions that take into account factors unique to the cancer context (e.g., oncologists, cancer centers, cancer societies, cancer support groups, other cancer care professionals). Finally, it will ultimately be very important to conduct research on knowledge translation to determine how best to put these exercise behavior change interventions into practice to help cancer survivors.

6.0. CLINICAL AND PUBLIC HEALTH IMPLICATIONS

The effectiveness of exercise as a supportive care intervention for cancer survivors will depend to a large extent on the motivation and adherence of participants to such a program. Based on the current evidence, cancer care professionals can expect that less than 10% of cancer survivors will exercise during treatments and between 20 and 30% will exercise after their treatments. These data indicate that unless behavior change interventions are provided, the majority of cancer survivors will not benefit from regular exercise. Strategies to assist cancer survivors in adopting and maintaining exercise can be developed based on current knowledge of the determinants of exercise in this population. The key point for cancer care and fitness professionals is that cancer survivors will have unique incentives, barriers, and preferences for exercise that will need to be taken into account when developing creative intervention strategies for this population.

The research on exercise determinants suggests that cancer care professionals need to help cancer survivors develop strong intentions (motivation) to exercise during and after their treatments. According to the TPB,[19] these intentions are best facilitated by strategies that will convince cancer survivors that exercise is beneficial and enjoyable (instrumental and affective attitudes), that they are capable of exercising (control and self-efficacy), and that important others in their life will encourage and support them (subjective norm). Underlying attitudes, perceptions of control, and subjective norms are the salient beliefs that cancer survivors have about exercise and these will be the primary targets of any exercise behavior change intervention.

Instrumental attitudes (perceived benefits) can be improved by targeting the known motives for exercise. As noted earlier, these motives may vary by cancer survivor group and treatment status. For example, for those on treatment some of the key motives seem to be that exercise will help them cope with their treatments, forget about their cancer and treatments, maintain a normal lifestyle, reduce fatigue, and stay strong and healthy. For those who have completed treatments, some of the key motives will be to reduce their risk of a cancer recurrence and other chronic diseases for which they are at risk, improve their immune function, improve energy levels and quality of life, and return to a normal lifestyle. As an example of how a key motive may vary for a particular cancer survivor group, endometrial cancer survivors may be particularly motivated to exercise for weight loss.

Affective attitudes (perceived enjoyment) can be improved by targeting aspects of the exercise prescription as well as the physical and social environment. In terms of the exercise prescription, the two key aspects from a motivational perspective are exercise type and intensity. Cancer survivors should be encouraged to select an exercise and intensity that they enjoy. For many cancer survivors, the preferred exercise will be walking and the preferred intensity will be moderate. In terms of the physical and social environment, one key component is to have an attractive physical environment. Cancer care professionals can suggest outdoor exercise in parks and trails or an attractive fitness center in the neighborhood. Nevertheless, many cancer survivors will prefer to exercise at home. If so, cancer care professionals might suggest neighborhood walking or, if home equipment is used, watching television or listening to music while exercising. In terms of social context, many cancer survivors (about 40%) prefer to exercise alone and this preference should be respected. Nevertheless, many will also enjoy group exercise programs, especially women, and these types of programs might be developed. The challenge for cancer care professionals is to create a welcoming and nonthreatening environment where cancer survivors feel comfortable in doing their exercise programs.

Perceptions of control or self-efficacy (perceived barriers) can be enhanced by helping cancer survivors anticipate and overcome the known barriers to exercise. Similar to the motives, the barriers will vary by cancer survivor group and treatment status. For those on treatment the primary barriers will likely be treatment-related side effects such as infections, nausea, diarrhea, and fatigue. As an example, strategies to overcome the barrier of fatigue may include suggesting low-to-moderate intensity exercise (e.g., 50–60% of maximal capacity), shorter duration exercise (e.g., 10 minutes at a time), interval exercise (i.e., alternating exercise and rest bouts), and/or exercising during days (e.g., not during chemotherapy week) and times (e.g., early in the morning) when fatigue is at its lowest. As a second example, strategies to overcome the barrier of diarrhea may include lower intensity and shorter duration exercise, not exercising after meals, and exercising in locations where washrooms are convenient and private (e.g., at home) rather than sparse and public (e.g., outdoor walking trails, fitness centers).

For those who have completed treatments, the primary barrier will likely be lack of time/too busy followed by experiencing a recurrence, fatigue, and comorbidities. Fortunately, there are many strategies for overcoming the time barrier. For example, exercise can be used as a form of transportation (e.g., walking or biking to work or shopping), it can be combined with other activities (e.g., watching television), it can be done in situations with a significant amount of waiting time (e.g., doctor's appointments, watching a child's sport activity, at an airport), and it can be done during lunch or coffee breaks.

Subjective norm (perceived approval and support) can be enhanced by enlisting the key people in the cancer survivor's life to provide support and encouragement. In general, the key people will be the spouse, family, and friends. These individuals should be informed about how important it is for them to encourage and support their loved one to exercise and to possibly even exercise with them. The cancer-specific key people will be the oncologists, nurses, cancer agencies, support groups, and other cancer survivors. Cancer care professionals should make it clear that they recommend exercise and perhaps even provide support in terms of facilities or space at the cancer center, equipment such as a home exercise equipment lending program, or by securing discounted rates or free passes to local fitness centers. Other cancer survivors who exercised regularly during their treatments might also be brought back as role models for the newly diagnosed cancer survivors to provide advice or even lead an exercise class if qualified.

7.0. SUMMARY

Research into exercise motivation and behavior change in cancer survivors is an important field of inquiry that promises to make a significant contribution to the health and well-being of cancer survivors. Presently, the studies are few in number and of modest quality but the research is increasing rapidly in terms of both quantity and quality. Preliminary research has suggested that exercise participation rates decline in cancer survivors during treatments to less than 10% and often do not return to prediagnosis levels even after treatments are completed. Perhaps 20–30% of cancer survivors exercise regularly after treatments. Theoretical models, such as the TPB, have proven useful in understanding this decline but further research is necessary. To date, there are few behavior change interventions that have been proven to increase exercise participation rates in cancer survivors. For now, fitness and cancer care professionals will have to rely on the general literature on exercise behavior change as well as their own creativity in developing effective exercise behavior change interventions in cancer survivors.

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Chapter 8

Fatigue

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1.0. INTRODUCTION

Despite many significant advances in cancer treatment and care, cancer remains the second leading cause of death in the United States.[1] Nevertheless, improvements in cancer treatment and care have led to a 50% increase in cancer survivorship, compared to 30 years ago.[1] Currently 62% of cancer survivors can now expect to live at least 5 years past their original diagnosis and there are almost 10 million cancer survivors in the United States.[1] As a result of this increase in survivorship the issues and problems facing cancer survivors, whether psychosocial or physical, assume increasingly greater significance, most importantly to the individual survivor, and also to the broader issue of public health.

Cancer-related fatigue (CRF) is a profound fatigue related to cancer or its treatment. This fatigue is recognized as a common and debilitating complaint among cancer survivors that has until recently been underappreciated by the medical community, though certainly not by the cancer survivor.[2,3]

As many as 76–99% of cancer survivors complain of this CRF.[2–5] Survivors report that CRF can be more distressing than pain or nausea and can significantly curtail activities of daily living (ADL), such as walking, cleaning, and running errands, and can diminish quality of life (QOL), including socializing, the ability to enjoy life, and emotional well-being.[2,3,6,7] This fatigue is not limited to the time during treatment and may persist for years after completing treatment.[8–14] Despite the increasing importance of this survivorship issue, it has been difficult to fully describe the fatigue of cancer and its treatment. One working definition provided by the National Comprehensive Cancer Network (NCCN) is that CRF is a "persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning."[15] Cancer-related fatigue is also recognized to be different than exercise-induced fatigue as it is greater in magnitude and persistence, it remains after periods of rest, and it is more severe and distressing then exercise-induced fatigue.[16–18] It can also be thought of as fatigue or tiredness greater than what would be expected for a given activity, whether physical or mental.[19,20] Because the exact cause of CRF is for the most part unknown, it falls under the"fatigue of unknown origin" category that is shared by many other immunological and neurological diseases, as well as a variety of other diseases and syndromes such as HIV infection, multiple sclerosis, chronic fatigue syndrome, Gulf War syndrome, etc.

Although much about CRF is not known it is generally accepted to be multifactorial with contributions from both psychological and physiological factors.[21–23] Discovering the specific etiology of CRF is complicated by this multifactorial nature. In addition, it is not clear if there is a distinct mechanism or set of mechanisms that causes this fatigue or if it is a consequence of the underlying pathophysiology of cancer, its treatment, or both. Furthermore, the determinants of CRF may be situational and differ across time depending on the type and stage of cancer, and treatment. This specificity of CRF may help explain some of the differences in the literature. For example, 60% to close to 99% of patients with a variety of cancers experienced CRF while undergoing radiation[13,24–28] or chemotherapy.[3,4,13,27,28] The degree of fatigue is somewhat dose-dependent in both cases.[8,11,13,20,24–29] The persistence of fatigue several months to a year after radiation or chemotherapy has been reported on the order of 30–40%.[10,13,30] Smets *et al.*[31] studied men with prostate cancer 9 months after radiation therapy. There was no significant difference in fatigue in the cancer survivors compared to a control group although both groups reported fatigue.[31] In contrast, other studies have reported CRF to be long-lasting when assessed years past successful treatment.[8,10–14] About 16–24% of testicular cancer and Hodgkins disease survivors reported CRF that was greater than fatigue measured in controls 12 years or more (~10–30 yrs) after treatment in cross-sectional and longitudinal designs, with greater severity reported by the Hodgkins disease survivors.[9,12,14] In describing CRF of long duration most are data from cross-sectional studies. Given the apparent chronic nature of CRF and its increasing prevalence, well-designed prospective studies are needed before the natural history of CRF can be confidently described. Determining the cause of CRF or any one of its components will greatly assist in specifically targeted treatment interventions and provide the framework for an optimal time course of intervention.

Treatment of a psychosocial or physiological mechanism may relieve in part or in its entirety the symptom of fatigue (e.g., refs. 22 and 32). Some of the psychosocial factors related to CRF include sleep and mood disturbances, chronic stress, anxiety, pain, cognitive disturbance, and depression.[33–35] These topics are covered in greater depth in other chapters and only depression will be reviewed with respect to CRF. Physiological factors specific to cancer that may contribute to CRF include cytokine production, altered hypothalamic–pituitary–adrenal (HPA) activation, cachexia, anemia, and neuromuscular dysfunction.[36–43] It is important to recognize that these factor designations are not all-inclusive nor are they independent. For example, increased cytokine production, whether tumor derived or from treatment could lead to cachexia or anemia, both of which could affect neuromuscular function. In addition cytokines could activate the HPA axis, which in turn could lead to depression. Complicating matters is the fact that combinations of factors leading to CRF are likely to be specific to the type of cancer as well as the type of treatment and may vary across time. The effects of treatment interventions, including radiation,[7,13,24–26,28] chemotherapy,[4,8,11,20,28] and biological response modifiers[44] are associated with their own specific psychosocial and physiological disturbances.

Fatigue Measurement: Just as CRF defies a simple definition so does its measurement or assessment. Unlike muscle fatigue, which can be objectively quantified, CRF is subjective and assessed with self-report survey tools or questionnaires.[21,23,45]

Unfortunately there is currently no single survey instrument to fit the needs of all those interested in CRF, whether this interest is from a clinical diagnostic or a research perspective.

To simply measure fatigue severity a unidimensional scale is often used. These can be fast and easy to administer in a clinical setting. These scales may include a one-word description of the fatigue (none, mild, moderate, severe), or a visual analog or Lickert type scale.[46] Fatigue may also be derived from a single question in a symptom checklist or from a multiquestion fatigue subscale of a larger survey such as the Fatigue Scale of the Profile of Mood States.[21] Another approach is one the NCCN has established as a clinical guideline for screening, assessment, and management of CRF which is based on three questions, on a 0–10 scale regarding the presence of fatigue and its functional impact.[47] While unidimensional measures of fatigue can have clinical significance, these measures do not always provide insight into the specific nature or mechanisms of fatigue that may differ widely between persons, treatment, or cancer type. In addition, the reliability and validity of some of these unidimensional approaches have been questioned.[29,46]

It is accepted that CRF is a multidimensional phenomenon that can include behavioral and physical dimensions, in addition to fatigue severity or impact.[21–23,32,37,48,49] As such, much effort has been expended in establishing multidimensional measurement tools. One of the first multidimensional instruments for measuring fatigue in cancer survivors was the Piper Fatigue Self-Report Scale,[50] which was validated in breast-cancer survivors and later revised.[23] The domains assessed included behavioral, sensory, cognitive/mood, and affective/emotional. Since the Piper Fatigue Scale, other validated multidimensional questionnaires have been used to characterize and measure various aspects of CRF.[21,45] Along with the dimensions of fatigue assessed, these include the Fatigue Symptom Inventory,[51] which assesses severity, frequency, diurnal variation, and interference; the Multidimensional Fatigue Symptom Inventory,[46] which assesses general, physical, emotional, and mental fatigue as well as vigor; and the Revised Piper Fatigue Scale.[23] For more specific information on these questionnaires and others see Jacobson[21] and Wu and McSweeney.[45]

In contrast to the simpler unidimensional surveys, most of these multidimensional tools can be more tedious and difficult for patients to complete but provide invaluable specific information to the clinician or researcher interested in the makeup of fatigue and how to best treat it. Because each instrument emphasizes different aspects of the fatigue experience, the choice of instrument is dependent on the specific questions being asked by the clinician or researcher. Jacobson[21] has summarized three additional important considerations in choosing a particular questionnaire: (1) The time frame during which the symptom of fatigue is queried. For example, 24 hours, 2 weeks, or 1 month. This would be particularly important for longitudinal assessment. (2) Whether or not the questionnaire is also valid for those not experiencing fatigue such as might be expected in a control group. (3) The population specificity of the instrument or whether the survey is valid for general use or only for specific populations.

2.0. MECHANISMS

Because CRF can affect functional activities and decrease QOL, investigating its mechanisms is not only warranted but imperative. In response to this challenge and in recognition of the increasing attention being paid to this area of concern, many excellent reviews have been published over the past several years summarizing the current state of knowledge in this area (e.g., refs. 20, 22, 32, 37, 39, 49, and 52). In the remainder of this chapter we will attempt to highlight some of the more common theories and views with an emphasis on the interrelation of causative factors. As a transition into the role of muscle function in CRF we will highlight the role of exercise as an effective treatment for CRF. Finally, we will expand upon the role of muscle function and other factors affecting energy production as potential components of CRF. In general, a role for altered muscle function in CRF has not been addressed in depth in previous reviews.

Depression: Depression is a mood disorder with emotional and physical symptoms, some of which are difficult to separate from CRF. The presence of depression in cancer survivors has been described as two to three times that in the general population.[53] The prevalence of major depression in the cancer population has been reported to be as high as 53%.[35,54–57] The physical and emotional symptoms of depression include fatigue, anorexia, changes in sleep patterns, decreased concentration, loss of interest, and feelings of hopelessness.[35,58] The prevalence of depression and its relationship to fatigue makes it a significant symptom in cancer survivors that warrants its own chapter in this volume.

The association between depression and fatigue may seem self-evident because fatigue is itself a symptom of depression, and it is difficult to separate fatigue from depression or other mood disturbances such as anxiety, or stress.[58–60] For example, in women with uterine cancer the correlation between depression and fatigue was $r = 0.71$.[61] Fatigue was also associated with higher levels of depression, pain, and sleep disturbance in breast cancer survivors,[10] with depression and pain being the strongest predictors of fatigue. The Fatigue Coalition Study reported that survivors who experienced fatigue on a daily basis were more likely to have reported depression than those reporting fatigue only a few days each month (32% vs. 14%).[2] For long-term survivors of testicular cancer, 10–30 years post-treatment, CRF was predicted by both depression and anxiety.[12] While it is tempting to suggest that depression or other "non-physiological" factors may be most important for the long-term cancer survivor, it has also been suggested that CRF in long-term survivors of Hodgkins disease is more strongly associated with physical, not psychological, well-being.[6] Proper management of fatigue in the long-term cancer survivor will be dependent on the ability to correctly separate the effects of depression from other factors affecting CRF.

Because fatigue is part of the symptomatology of depression it is not surprising that significant correlations have been reported between fatigue and depression. It is this overlapping symptomatology that makes delineating the independent contribution of depression to CRF so difficult. This difficulty is compounded by the multifactorial nature of both depression and fatigue. As an example, if fatigue results purely from a chronic medical condition such as cancer or neurologic disease then depression scales that do not adequately differentiate physical or vegetative from psychological symptoms, such as mood, may overestimate the degree of depression or fail to provide a clear rationale for treatment.[62] Thus, while it is clear that there is an interrelationship between fatigue and depression, some cognitive, emotional, and interpersonal symptoms are more specific to clinical depressive disorder than CRF.[58] These factors include self-devaluation, sense of a threatening future, hostile and frightening surroundings, and the emotional symptoms of emptiness and deadness.[58] Therefore, it is just as critical to recognize and measure depression as a multidimensional construct as it is to measure fatigue as such.

Finally, as difficult as it may be to separate fatigue from depression, it has to be emphasized that depression and CRF are not synonymous. For example, breast cancer survivors receiving chemotherapy who received the serotonin reuptake inhibitor paroxetine showed a decrease in depression but no change in CRF.[63] In both breast cancer[25] and prostate cancer[24] survivors treated with radiation therapy, CRF was reported in the absence of depression. It can be concluded from these studies that fatigue, at least during radiation therapy, may be independent of depression. However, these earlier results differ from some of our own preliminary work that showed a significant correlation between depression and CRF after but not before radiation therapy in prostate and lung cancer survivors.[42]

While the relationship between depression and cancer is readily acknowledged, this does not imply causality or directionality. While depression may contribute to fatigue the converse may also be true. Fatigue, due to cancer or its treatment, and independent from depression, may itself contribute to a component of depression directly or secondarily through decreased QOL, deconditioning, or other related physical or psychological factors. Finally, depression and fatigue could both be secondary to some other common precipitating factor such as an altered hypothalamic–pituitary–adrenal axis (HPA axis) activation.[32,59,64] Altered HPA function could occur from changes in cytokine production or as a reaction to stress or anxiety. Clearly, the relationship between depression and CRF is complex and it forms the basis for ongoing research.[58,59]

Cytokines: Cytokines are polypeptide mediators involved in cellular communication, generally associated with functions of the immune or inflammatory process. They are released primarily by activated monocytes and macrophages as well as tumor cells or could result from exogenous treatment.[38,44,65] The most commonly cited cytokines with purported involvement in CRF are pro-inflammatory and include tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferons.[38] There exists a normal balance between cytokines and their antagonists. This balance can be disrupted with cancer or its treatment leading to excessive production. Cancer, like other chronic inflammatory processes, is mediated by endogenous cytokines, and dysregulation in their production can cause activation of the HPA axis or fatigue.[38,66–69] A role for cytokines in CRF is strongly indicated because cytokines have been implicated in depression,[66,67] alterations of HPA axis activation,[67,68] cachexia,[38,40] and anemia.[38] As with depression, altered HPA axis activation, cachexia or muscle wasting, and anemia may be important mechanisms of CRF.

Hypothalamic–Pituitary–Adrenal Axis: A hypothesis that has recently been receiving well-deserved attention is that an altered hypothalamic-pituitary-adrenal axis may be responsible for both depression and fatigue resulting from cancer or its treatment.[32,59] This hypothesis is theoretically grounded because hypercortisolemia resulting from increased HPA axis activation can be associated with depressive illness[64,70,71] as well as with fatigue in some neurologic disease.[72] However, any relationship between an altered HPA axis and fatigue is not straightforward because in the chronic fatigue syndrome, the symptom of fatigue tends to be associated with hypo- not hypercortisolemia.[73] Thus, a relationship between HPA axis dysfunction and fatigue could be from hyper- or hypocortisolemia. This example also illustrates that care must be taken when comparing CRF to the fatigue syndromes of other pathologies associated with fatigue of unknown origin.

Excessive HPA axis activation in cancer survivors is intriguing because it could arise from a generalized stress or anxiety response (see Chapter 10, 19) with concomitant activation of the sympathetic nervous system.[67,74] In this way HPA axis activation may be a precipitating mechanism for the fatigue associated with stress or anxiety. Alternatively the HPA axis could be activated by pro-inflammatory cytokine production.[67,69,74] Yet another role for an altered HPA axis in CRF is thorough cytokine-mediated sleep disturbances.[75] Disturbed sleep can lead to fatigue in cancer survivors as well as the general population, whether through an altered HPA axis or not (e.g., depression, anxiety, etc.).[33,34,76] Evidence that HPA axis dysregulation is associated with CRF is provided by evidence in breast cancer survivors 1–5 years after initial diagnosis with completed therapy.[77] In these studies CRF was associated with both a flatter diurnal cortisol slope and less rapid evening cortisol decline even after controlling for depression.[77] Thus, there may be an important role for altered HPA axis activation in long-term cancer survivors even after the acute effects of treatment are resolved. Cancer-related fatigue is also associated with depression and anxiety in long-term survivors of testicular cancer.[12] Cortisol was not measured in these cancer survivors but stress, anxiety, or other psychological distresses are common triggers for HPA axis activation and these factors are also associated with depression. Stress and anxiety specifically related to cancer can include chronic fear of recurrence.[78–80] The relationship between HPA axis activation and CRF in long-term cancer survivors is clinically relevant and more studies in long-term cancer survivors with CRF are warranted.

Cachexia: Cachexia is a wasting syndrome comprised of both muscle wasting and a decrease in adipose tissue. It affects about 50% of all cancer patients,[40] is a hallmark of advanced cancer, and can lead to decreased overall survival.[40,81] Cachexia is a significant deleterious consequence of cancer or its treatment in its own right, with its own extensive body of literature (e.g., refs. 40 and 82). In addition, muscle weakness resulting from the cachexia of cancer has been hypothesized to contribute to CRF.[81,83] Muscle wasting and weakness require a person to exert a greater percentage of his maximal force compared to non-cachexic muscle to generate adequate contractile force during ADL. This additional effort may contribute to the symptom of CRF. Loss of muscle protein resulting in cachexia can occur whenever there is an imbalance between anabolic and catabolic processes in the muscle, such that muscle anabolism is diminished, catabolism enhanced, or both.

Decreased anabolism can occur with anorexia or otherwise poor nutritional status and decreased caloric intake, or decreased physical activity.[82] Decreased caloric intake, anorexia, or poor nutrition from whatever origin (e.g., depression) is often discussed in the context of cachexia, but it is important to recognize that these factors may lead to CRF independently. Nevertheless, while anorexia or decreased nutritional intake is thought to influence cachexia it cannot fully explain the loss of protein and lipid stores resulting in weight loss.[40] If food intake is a primary factor that contributes to cachexia, then supplementation should reverse or attenuate the muscle loss. Human studies have shown that cachexia is not fully reversed by dietary counseling,[84] nutritional supplementation,[85] or total parenteral nutrition.[86] In addition, there is temporal dissociation between cachexia and anorexia such that cachexia has been reported to preceded anorexia.[87]

Increased catabolism can occur with poor nutritional status and a chronic decrease in physical activity.[82] In addition, pro-inflammatory cytokines and tumor-derived factors can have a catabolic effect.[38,40,82] Much of the experimental evidence for the role of pro-inflammatory cytokines in cachexia centers around the previously described TNF-α, IL-1, IL-6, interferon γ (IFN- γ), and leukemia-inhibitory factor.[40,82,88] If the cachexia-induced changes in body composition lead to increased

CRF then another role for cytokines in CRF can be identified. The role of cytokines in cachexia is supported by studies where the infusion of pro-inflammatory cytokines into animals leads to muscle wasting with increased catabolism and decreased anabolism.[89] While cytokines may be important in the development of cachexia, no single factor can fully explain the cachexia observed in cancer patients.

Anemia: Anemia is a reflection of inadequate hemoglobin concentration in the blood and can result from cancer or from its treatment, due to bleeding, hemolysis, or increased cytokine production.[36] These effects can be compounded by any nutritional deficits. Anemia can be broadly defined as hemoglobin levels less than 12gm/dL in the blood, although some sources will cite normal values for women 12–14 gm/dL and men 14–15 gm/dL.[38] Symptoms of anemia include fatigue, lethargy, decreased exercise tolerance, decreased endurance, and shortness of breath. The anemia seen in cancer patients can result from the disease itself or the myelosuppresive effects of intervention. The normal negative feedback resulting in an erythropoietin-mediated hemopoietic response is often blunted in the anemia of cancer.[38] This may be compounded in part by the pro-inflammatory cytokine-mediated suppression of red blood cell production.[38] This cytokine-mediated mechanism results in the inability of the body to respond sufficiently to anemia. This also provides yet another role for cytokine regulation or dysregulation in CRF.

Of all the purported mechanisms of fatigue, anemia is considered to be of known origin as it has one of the most direct and commonly accepted negative effects on fatigue or energy, at least as it pertains to oxygen-dependent mechanisms. In addition, it may be one of the most common known conditions clearly associated with CRF.[90] Historically, treatment of anemia with blood transfusion has usually not taken place until hemoglobin falls below 8gm/dL,[36,38] despite the observation that symptoms often appear at levels between 8–10 gm/dL. When anemia caused by chemotherapy is reversed with epoeitin alfa, a recombinant human erythropoietin, both fatigue and QOL improves.[36,91,92] However, anemia does not fully account for the severity of CRF.[93] Of particular interest is recent work in mice that has shown that erythropoietin not only promotes erythrocyte production but also attenuates cachexia by way of decreased IL-6.[94]

Exercise Intervention: While the fatigue associated with anemia has clear therapeutic indications, exercise is one of the few effective nonpharmacological treatments for CRF.[22] Research consistently supports the use of exercise as a countermeasure to the symptomatic fatigue of cancer,[22,95–97] although the mechanisms by which this intervention occurs are not entirely clear. One mechanism by which exercise may improve CRF is through its beneficial effect on negative mood states, such as depression or anxiety.[98–100] Although aerobic exercise has typically been used as an intervention, improvements in depression can be independent of any increase in aerobic capacity,[99] as might be expected with short-term, low intensity, or resistance exercise. Exercise may have positive effects on immune function (e.g., cytokines),[101–103] although this is controversial and any significance to CRF is unknown at present.[101] Another mechanism by which exercise decreases CRF is by promoting improvements in or maintenance of muscle function. For example, appropriate exercise could be an effective countermeasure to cachexia-induced weakness through promotion of increased muscle mass.[81,104] Exercise could also help counteract anemia-related endurance decreases by increasing oxidative or aerobic capacity. Thus, exercise may exert a beneficial effect on CRF or QOL through changes in muscle function in addition to any improvement in depression or other psychological manifestations of CRF. The specific impact of exercise is covered elsewhere in this volume.

The potential for exercise to benefit CRF through an improvement in muscle function has not attracted much attention and forms the rationale for much of the balance of this chapter. Although the beneficial effect of exercise on CRF is consistent there are many questions that remain to be answered to improve the effectiveness of this important intervention. Among these questions are what is the best mode (e.g., resistance or aerobic exercise), intensity, frequency, and duration of exercise for a particular type of cancer, stage, treatment, or time from treatment. The importance of exercise to cancer survivors cannot be stressed enough. The benefits of regular exercise transcend the context of fatigue, as exercise may decrease overall health risk associated with inactivity. Separate chapters are devoted to this timely topic (see Chapter 7, 15).

3.0. NEW DIRECTIONS

3.1. Neuromuscular Function in Cancer-Related Fatigue

Despite the increasing body of research into the overall symptom of fatigue (i.e., CRF) in cancer survivors, muscle fatigue per se has attracted little attention.[41–43,105] This is somewhat surprising because muscle fatigue is readily quantifiable and may contribute to or result from CRF. Although it may seem self-evident that muscle fatigue would be a component of the overall symptom of fatigue, such an association has not always been apparent in other chronic diseases presenting with fatigue of unknown origin such as in multiple sclerosis.[106,107]Thus, it is not known if muscle fatigue in cancer survivors is related to CRF, or if muscle fatigue should be considered an independent clinical or functional entity important in its own right, because adequate muscle capacity is important in ADL, as well as in many recreational pursuits.

Definitions: Although CRF is not so easily defined, muscle fatigue can be defined as a loss of the maximal force generating capacity of muscle.[108] This is often indicated by decreased maximal voluntary contraction (i.e., strength) after a fatigue inducing exercise protocol. Endurance is functionally related to muscle fatigue, and can be defined as the time to which a submaximal task can no longer be performed.[109] These two processes are reciprocally related where increased muscle fatigability results in decreased muscle endurance.

Pathway of Force Production: A conceptual model by which to study muscle fatigue in cancer survivors is the “pathway of force production.”[110] This model recognizes that the initial signal for muscle contraction is initiated centrally in the motor cortex. Neural transmission continues down the spinal cord and out to the muscle where neuromuscular transmission occurs. These brain and spinal processes are considered central activation and the events downstream from the spinal cord can be considered peripheral activation. Successful neuromuscular transmission leads to excitation of the sarcolemma, excitation contraction-coupling and ultimately cross-bridge formation and movement resulting in muscle contraction. Intramuscular oxidative energy for the contraction process occurs in the mitochondria and is dependent on the integrity of the electron transport chain as well as on adequate oxygen delivery by the cardiovascular system. If there is a limitation, impairment, or failure along any single site or multiple sites of this pathway then muscle fatigue could result.

Central Factors Affecting Muscle Fatigue: Central neural activation contributions to muscle fatigue can be assessed in its simplest form by comparing changes in maximal voluntary contraction, or strength, to contractions produced by electrical stimulation of a peripheral motor nerve or muscle. This is typically assessed before and after a fatiguing contraction. The electrically evoked contraction is a measure of peripheral muscle function because it activates the muscle independently and downstream from the central motor command. If, after a fatiguing contraction, the loss of voluntary force is proportionally greater than the loss in electrically stimulated force then central activation impairment is thought to have occurred, although the exact mechanism for this impairment may not be known. Another common method of assessing central activation impairment is by supramaximal stimulation of a muscle or its nerve, during a maximal contraction. If additional evoked force is superimposed on the voluntary contraction during supramaximal stimulation then incomplete activation of the muscle is thought to have occurred.[110,111] Several variations on this technique are in use, including the interpolated twitch[111,112] and the central activation ratio.[110] Because the surface electromyogram (EMG) can provide general insight into central neural drive, various indices of the EMG have also been used to indicate central neuromuscular function.[105,113] More direct measures of central activation include transcranial magnetic stimulation and recording of the electroencephalogram (EEG).

Many of the factors previously discussed as being important in CRF could potentially result in central activation impairment in cancer survivors. Of particular interest is whether or not centrally mediated muscle fatigue results from fatigue caused by depression, anxiety, lack of sleep, or stress. A correlate of depression could be decreased motivation to maintain a contraction, in which case a central activation limitation would result in decreased endurance. Conversely, decreased endurance or increased muscle fatigue might contribute to depression or CRF which might initiate a positive feedback loop leading to even greater central activation impairment, greater depression, greater fatigue, and so forth. Central activation impairment could also be hypothesized to result in a more direct fashion such as by neural damage, as could be caused by radiation or surgery.[114–116]

Peripheral Factors Affecting Muscle Fatigue: Peripheral muscle activation is most commonly assessed with electrical stimulation of a muscle or its nerve and electromyography. For example, changes in the compound muscle action potential, or M-wave, can be assessed to indicate alterations in neuromuscular transmission or sarcolemmal excitation.[108,110] Muscle metabolites can be measured directly by muscle biopsies and biochemical analyses. A noninvasive in vivo technique with which to study intramuscular metabolism is ^{31}P magnetic resonance spectroscopy, which can measure phosphorus-related energy metabolites (e.g., PCr, Pi, ATP, H^+) in conscious humans at rest or during exercise.[117,118]

There are many factors thought to contribute to CRF that could also affect peripheral muscle function. As with the central nervous system, direct damage to the peripheral nerves[114,116,119]could affect neural or neuromuscular transmission. Cachexia can result in decreased muscle mass and strength as well as other changes in muscle composition.[40,81,88] These changes in muscle could result directly or indirectly in muscle fatigue. A direct effect would be through any biochemical change affecting contractile mechanics. An indirect effect has been described earlier whereby muscle weakness, as opposed to muscle fatigue per se, could result in increased muscle fatigue by virtue of having to perform a given amount of work with a smaller or weaker muscle. Anemia would have a direct effect on oxygen delivery to muscle resulting in decreased muscle endurance. Such an oxygen limitation to peripheral muscle function would also be manifested as a decreased whole body maximal oxygen uptake and resultant systemic fatigue. Finally, decreases in chronic physical activity, as could occur with increased CRF or depression, could result in muscle changes consistent with other conditions of muscle disuse or deconditioning resulting in decreased muscle endurance and strength.

Muscle Fatigue in Cancer Survivors: The few studies that have specifically quantified neuromuscular function in cancer survivors have all reported results consistent with increased muscle fatigue[42,43] or other neuromuscular changes.[105] In breast-cancer survivors undergoing chemo- or hormonal therapy, with radiation therapy, Bruera and colleagues[41] documented increased muscle fatigue in the adductor pollicis muscle after 30 seconds supramaximal electrical stimulation compared with control subjects. This increase in fatigue was independent of strength which was similar in the survivors and control group.[41] These results are consistent with a peripheral origin of muscle fatigue but neither central activation nor CRF was measured.

In prostate cancer patients undergoing radiation therapy, Monga *et al.*[105] examined the force/EMG ratio during fatiguing high intensity isometric contractions of the tibialis anterior before, at 8 weeks of radiation therapy and 6 weeks after therapy. They found evidence of a decrease in the force/EMG ratio before the isometric contraction (i.e., unfatigued) at 8 weeks of radiation therapy compared to the same condition both before and after therapy. This change suggests that a greater neural drive was required for a given force production during treatment, not lesser as might be interpreted. As would be expected, the force/EMG ratio decreased as a result of the fatiguing exercise under all three conditions but the decrease was apparently similar under all conditions (i.e., pre-therapy, during therapy, post-therapy). Thus the significance of an altered force/EMG ratio (during radiation therapy) was unclear and not necessarily related to muscle fatigue. Interpretation of this study was difficult due to the small number of subjects studied and lack of a control group. In this same study, radiation therapy did not result in changes in CRF, depression, or sleepiness all of which were apparently within normal limits.[105]

Ranganathan and colleagues[43] have recently reported decreased endurance of the elbow flexors in 16 cancer survivors with advanced lung, breast, or gastrointestinal cancer reporting fatigue compared to a healthy control group. Cancer survivors were also weaker and had evidence of neuromuscular transmission impairment, as well as central changes in the EEG compared to control.[43] It was unclear however if the EEG changes were related to muscle fatigue or CRF.

In our own laboratory,[42] we observed that radiation therapy in prostate cancer survivors resulted in significantly decreased muscle endurance at 6 weeks of therapy compared with pretherapy and to a non-cancer control group. Strength was similar in survivor and control groups and the survivor group reported significantly greater CRF measured by the revised Piper Fatigue Scale.[23] Muscle testing consisted of intermittent isometric contractions of the tibialis anterior at 40% Maximal Voluntary Contraction (MVC) until task failure. Muscle fatigue at task failure was similar in both cancer survivors and control subjects. Central activation measures were also similar between groups. To support an association between CRF and muscle fatigue, endurance time in the cancer survivors after radiation therapy was significantly correlated to the sensory subscale of the revised Piper Fatigue Scale.[23] The sensory subscale measures severity of the physical intensity of fatigue.[23] Together, our data showed a decrement in muscle endurance but not strength. These data provide further evidence for peripherally mediated muscle fatigue associated with radiation therapy. The pattern of decreased endurance despite a similar loss in maximal force generating capacity can be interpreted as cancer survivors fatiguing to a similar physiological endpoint, but at a faster rate than control subjects, consistent with decreased oxidative capacity. If true, decreased intramuscular oxidative capacity could arise from changes in the mitochondrial respiratory or electron chain enzymes or secondarily from the effects of muscle deconditioning.

Although limited, what little data are available provides some evidence for a relationship between muscle fatigue and CRF, thus providing further rationale for exercise as management of CRF. Certainly more targeted research is warranted in this area of inquiry.

Mitochondrial Alterations: Impairment in mitochondrial function could result in defective ATP production which has been hypothesized to contribute to the decreased energy reported by those with CRF.[39] Mitochondria are unique in that they have their own genome. This mitochondrial genome (mtDNA) is particularly prone to DNA damage and point mutations have been reported to be greater in muscle biopsies of cancer survivors who have been treated with whole body radiation as well as chemotherapy compared to control subjects.[120] Such point mtDNA mutations could lead to mitochondrial myopathies resulting in impaired electron transport chain function and decreased muscle oxidative capacity.[121] Whether or not such mitochondrial alterations contribute to muscle or CRF in cancer survivors is intriguing and awaits further research.

Physical Activity: Decreased physical activity or deconditioning is an important consequence of and contributor to both CRF and muscle fatigue. Separate Chapter 5 in this volume discusses physical activity in cancer survivors in more detail (see Chapter 7, 15). Briefly, in addition to increasing overall health risk independent of cancer or its treatment, decreased physical activity can initiate a positive-feedback chain of events whereby decreased physical activity could further exacerbate CRF, muscle fatigue, or depression. Evidence for this is provided by the inverse relationship between fatigue and physical activity, as quantified by accelerometers, reported in cancer survivors undergoing chemo- or radiation therapy; the lower the physical activity the greater the fatigue.[122,123] Decreased physical activity may be a particularly important factor in the CRF of long-term survivors especially if such behaviors were previously acquired in response to cancer or its treatment. In the absence of mitigating factors, education and exercise could successfully reverse any CRF caused by inactivity per se.

Autonomic Cardiovascular Function: Optimal muscle endurance is dependent on adequate oxygen delivery. While the importance of anemia cannot be overstated, a potentially overlooked contributor to CRF is impaired cardiovascular autonomic function. The rationale for this hypothesis is that muscle fatigue could arise from any limitation to muscle perfusion or oxygen delivery. In addition, any impairment in autonomically mediated cerebral blood flow could result in the symptom of fatigue independently of any contribution to muscle fatigue. Fatigue is symptomatic of neurogenic hypotension and abnormal baroreflex-mediated orthostatic tilt tests have been implicated in the fatigue associated with the Chronic Fatigue Syndrome.[124,125] Baroreflex regulation has been shown to be severely impaired in cancer survivors who have received neck irradiation.[115,126] Based on these findings, it could be hypothesized that CRF would be greater in those with more impaired baroreflexes. However, fatigue was not measured in these previous studies in cancer survivors,[115,126] and it is not known whether or not impaired baroreflexes are associated with CRF in cancer survivors. There is also evidence that cardiovascular autonomic abnormalities, including tests of baroreflex and exercise function, may be more common than previously thought in survivors with advanced primarily breast, lung, or prostate cancer.[127,128] Again, because CRF was not assessed in these previous studies the

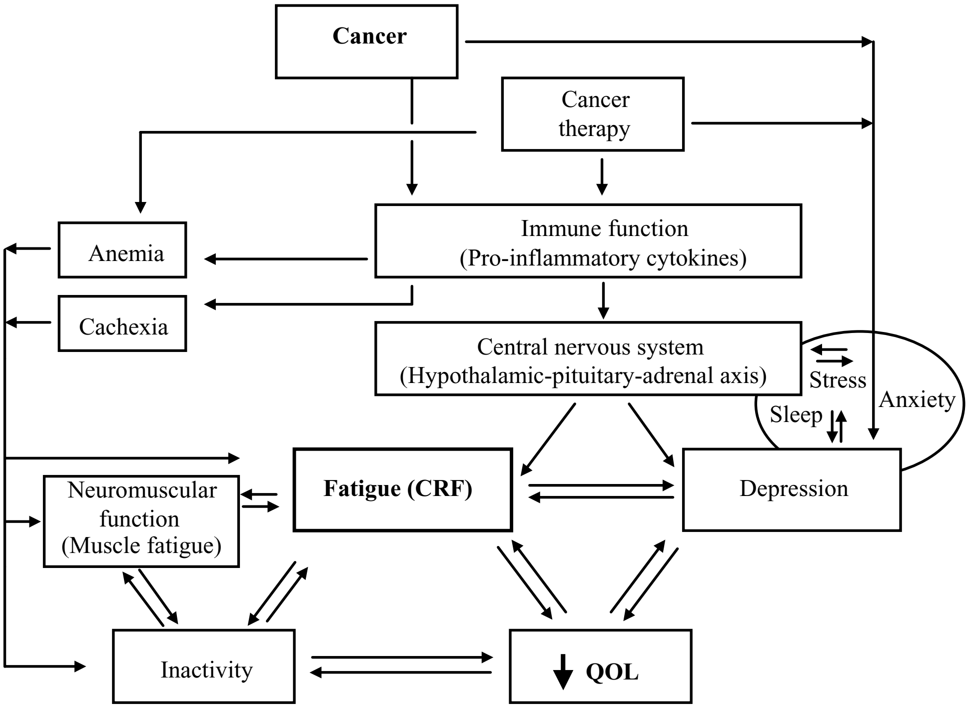

Figure 1. A Cascade of Multiple Factors Leads to Cancer-Related Fatigue (CRF) and Decreased Quality of Life (QOL). (Modified from Morrow.[32] For clarity only the factors discussed in this chapter are illustrated.)

functional significance of these abnormalities is unclear. To date autonomic cardiovascular regulation has not been adequately studied as an indication for, or mechanism of, CRF as it has in other diseases presenting with symptomatic fatigue.[118,124,125]

Closing Remarks: We have highlighted some of the more prominent theories regarding the origin of CRF and suggested new areas for future consideration, such as neuromuscular or cardiovascular autonomic function. We have found the conceptual model of CRF presented by Morrow[39] to be useful in our own understanding of CRF and we have modified it as Figure 1. In this model, cancer and its treatment set off a cascade of events often initiated by the action of cytokine production but ultimately leading to increased CRF and decreased QOL in the cancer survivor. As this cascade progresses there is an increasingly complex and often bidirectional interplay of fatigue-causing factors. For example, muscle fatigue or depression could contribute to CRF or in turn be affected by it. It is hoped that the increasing awareness of CRF will stimulate additional research into this, until recently, significant but underappreciated aspect of cancer survivorship. Only when a more precise understanding of CRF and its mechanisms are known can more targeted interventions be employed at appropriate times.

From a more global clinical and research perspective, significant symptomatic fatigue of unknown and known origin is characteristic of many immunological, neurological, cardiovascular, or infectious diseases such as chronic fatigue syndrome, multiple scleroisis, HIV infection or AIDS, fibromyalgia, or stroke. For the most part each has its own body of literature and measurement instruments. Because many of these disorders likely share common mechanisms of fatigue, interdisciplinary study across diseases, including cross-validation of fatigue surveys, must be facilitated so as to profit from already established knowledge and to aid in understanding the nature of fatigue in a particular patient population.

While CRF is a well-accepted consequence of treatment, it is now clear that a significant proportion of long-term cancer survivors are affected by this troubling symptom.[9,12,14] Perhaps the most overriding priority is to develop an understanding of how mechanisms of CRF may change across time for a specific cancer type, stage, or treatment. Prospective studies will ultimately be required but cross-sectional studies with appropriate control will also greatly aid our understanding of CRF in cancer survivors.

In this way treatment could be specifically targeted whether this be through psychotherapy, pharmacology, nutritional support, biobehavioral interventions, specific exercise prescriptions, or complimentary and alternative medicine.

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Chapter 9

Pain

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1.0. INTRODUCTION

Pain has been studied in patients with advanced cancer, but not generally studied during the extended period of cancer survivorship. Comprehensive review articles are silent about pain in cancer survivors.[1,2] There appears to be a widespread lack of knowledge and recognition of common pain syndromes. Yet many cancer survivors live and deal with pain on a regular basis. The incidence and types of pain vary with the cancer and sometimes with treatment modalities. In some groups of patients, pain can be severe and affect quality of life. Clinical experience suggests that pain in cancer survivors can be as debilitating as it is in cancer patients.[3] Survivors are defined as those who have completed their major course of treatment for cancer and are considered to be stable with regard to the cancer. Included are patients who still have evidence of tumor or who are at risk for recurrence.

2.0. EFFECT OF PAIN ON QUALITY OF LIFE

As indicated in other chapters in this book, a major source of information for studying cancer survivors are quality of life surveys. Many quality of life instruments have a pain item. While the focus is not on pain, studies in different groups of cancer survivors have found relationships between pain and lower quality of life. Some of these studies are summarized below.

2.1. Pediatric Solid Tumor Survivors

In one study of 220 survivors, participants completed the EORTC QLQ-C30 and the Ferrans and Powers Quality of Life Index for Cancer.[4] Back pain was reported by patients with osteosarcoma who had undergone amputation of an extremity and Wilms tumor patients who had received abdominal radiation therapy. Multiple models to predict quality of life showed that pain ($\beta = -0.10$ to -0.13, $p < 0.01$); dyspnea

($\beta = -0.22$ to -0.29; $p < 0.01$), and measures of toxicity had a negative effect on both measures of quality of life.[5]

2.2. Head and Neck

In a study of quality of life in 204 long-term survivors, patients completed the EORTC QLQ-C30, and the General Health Questionnaire,[6] a screening tool for psychological symptoms. Psychological distress was found in 30% of the patients and the presence of a high level of pain was significantly related to psychological distress ($\beta = 5.7$).[7]

2.3. Breast Cancer Survivors

In one study of 222 survivors who had undergone axillary lymph node dissection as part of breast cancer surgery, 72% reported shoulder arm pain. Present pain intensity was a significant predictor of quality of life measured by the EORTC QLQ-C30[8] with ($\beta = 0.29$; $p < 0.001$). Pain discomfort affect ($\beta = 0.42$; $p < 0.001$), sensation of pain ($\beta = 0.289$; $p < 0.001$), and pain disability for self care ($\beta = 0.261$; $p < 0.001$) were important predictors of psychological distress as measured by the Mental Health Inventory.[9,10] In another study, 55 survivors were surveyed with a health-related quality of life instrument, the RAND-36,[11] at a mean follow-up of 2.7 years from surgery, 60% reported pain and reduction of grip strength. Shoulder pain was a significant factor for the domains of social functioning ($\beta = -2.9$; 95% CI: -5.0, -0.8), mental health ($\beta = -2.3$; 95% CI: -4.1, -0.5), vitality ($\beta = -3.8$; 95% CI: -5.8, -1.8), pain ($\beta = -0.55$; 95% CI: -7.1, -3.9), health perception ($\beta = -4.5$; 95% CI: -6.3, -2.7), and health change ($\beta = -3.8$; 95% CI: -6.3, -1.3).[12]

In related investigations, researchers studied utility values for 692 survivors of breast, colon, melanoma or lung cancer who participated in the 1998 National Health Information Survey. Utility scores were generally lower in the acute period within 1 year of diagnosis, and were highest in the period greater than 5 years from diagnosis. Pain was a significant negative predictor of utility in long-term survivors of breast cancer ($\beta = -0.06$; 95% CI: -0.11, -0.012), colon cancer ($\beta = -0.13$; 95% CI: -0.23, -0.03), and lung cancer ($\beta = -0.21$; 95% CI: -0.37, -0.05). The other negative predictors were comorbid medical conditions.[13]

How pain affects quality of life in cancer survivors is an area for further study. The significance of pain to cancer survivors was explored in Gil *et al.*[14] In the current paradigm of the symptom experience, perception of the symptom leads to a cognitive response (symptom recognition), which in turn may generate an emotional response (distress).[15] Distress in turn then affects quality of life. Further understanding of the associations between pain and quality of life in cancer survivors will enable the development of interventions for both the pain itself and quality of life.

3.0. EPIDEMIOLOGY OF PAIN IN CANCER SURVIVORS

While surveys have not been done specifically for pain, some information can be gleaned from quality of life surveys of cancer survivors. Information on the prevalence of pain in cancer survivors is sometimes contradictory. In some studies the prevalence of pain may actually be lower than in a control group, and may differ between studies. There are a number of possible explanations. Recruitment strategies may be different, leading to different populations studied. As many pain syndromes can result from specific cancer treatments, the prevalence of pain syndromes may be affected by the era in which the patient was treated. The response rates vary between surveys. It should also be noted that surveys rely on self-report with additional professional pain assessments only done rarely. How patients interpret the survey questions can affect the response. Consequently, the prevalence of cancer-related pain in survivors, and how that relates to other common pain complaints, is difficult to discern at this point.

In this section, we will present data from larger surveys of survivors. Surveys limited to survivors by disease site will be summarized elsewhere in this chapter.

One of the first surveys was of 687 members of the National Coalition for Cancer Survivorship, where 81% of the respondents were women, breast cancer was the most frequent diagnosis (43%), and the median time from diagnosis was 80 months, the scores for physical well-being were lowest of the different quality of life domains, and both fatigue and aches/pains were rated by respondents as affecting their physical well-being. Interestingly, living with a spouse, being more than 5 years after diagnosis, and a higher income level were ameliorating factors.[16]

In a survey of 9535 survivors of childhood cancer, the prevalence of pain attributed to cancer or its treatment was 10.2%. Patients at increased risk were those with age greater than 24 years at interview, income of less than $20,000/year (OR = 1.8; 95% CI: 1.5–2.1), education of high school or less (OR = 1.4; 95% CI: 1.2–1.6), and diagnoses of sarcoma (OR = 1.9, 95% CI: 1.5–2.3) or bone cancer (OR = 3.1; 95% CI: 2.5–3.8) were at increased risk for pain. Patients with a diagnosis of Hodgkin's disease were at decreased risk (OR = 0.7; 95% CI: 0.6–0.9). Patients who had received radiation therapy had an increased odds ratio varying from 1.5 to 3.4 depending on the region radiated. This was not found for surgery or chemotherapy. The authors noted the difficulty in evaluating somatic complaints as a significant percentage of survivors of sarcomas and bone tumors experience cancer-related anxiety and fears, and therefore the need for a multifaceted approach to evaluation in order to determine those factors that affect pain in individual survivors.[17]

For older adults, a survey of 321 survivors (mean age 72 years, average period of time from diagnosis 10 years) randomly selected from a tumor registry of a cancer center found that out of 22 possible symptoms, the average number was 3.5 (SD = 2), and one symptom was attributed to cancer or its treatment. The most common symptom was pain, present in 31% and attributed to cancer by 21% of the patients with pain. By primary site, pain was reported by 42% of patients with breast cancer, 27% of patients with colorectal cancer, and 20% of patients with prostate cancer. Pain was attributed to cancer by 29% of the patients with breast cancer, 11% of the patients with colorectal cancer, and 11% of patients with prostate cancer. The number of years since diagnosis was inversely correlated to the association of a symptom with cancer, and the number of symptoms was correlated both with the number of types of treatments, and with having received chemotherapy.[18] In another survey of 964 older cancer survivors compared to 14,333 control patients, cancer survivors were more likely to experience arthritis (69% vs. 59%, $p < 0.001$) and to report frequent pain (36.4% vs. 29%, $p < 0.005$).[19] Other quality of life surveys show that in certain types of cancer, such as testicular and cervical cancers, survivors report less pain than control groups.[20,21]

From these studies, we can conclude that a significant fraction of cancer survivors experience pain which they attribute to their cancer or its treatment. There are data to indicate that a high-risk group of survivors for cancer-related pain are within 5 years of treatment, have a lower socioeconomic status, and are more likely to have undergone intensive treatments.

Much remains to be learned regarding the epidemiology of pain in cancer survivors. While healthy controls report a similar prevalence of pain, the type, quality, and the impact of pain may differ in cancer survivors

4.0. ASSESSMENT OF SURVIVORS WITH PAIN

When evaluating pain in patients with a history of cancer, the differential diagnosis includes:

Pain resulting from damage caused by the original tumor, often nerve damage.
Pain from treatment-related toxicity (e.g., surgery, radiation, chemotherapy).

Especially in the case of radiation therapy, pain as a manifestation of delayed toxicity may present years to decades later.

Pain from malignancy—a new malignancy or relapse of primary cancer.
Pain from new non-malignant disease.
Pain from comorbid non-cancer conditions.

The first step in management is to be aware of the problem and take it seriously. One common complaint of cancer survivors is that their pain complaints are not heeded. Acknowledgment and explanation by themselves can be very reassuring. Much of this chapter is devoted to descriptions of pain syndromes reported in survivors of different cancers to assist the reader in recognizing the various pain syndromes among cancer survivors. The second step is to acknowledge that at this point very little good evidence is available for treatment of the types of cancer-related pain syndromes. This is not surprising when one considers that the evidence base for treatment of pain in cancer patients is also weak.[22] Finally, it is essential that we recognize that as treatments for cancer change and progress, and the natural history of disease is altered, new types of pain syndromes may emerge in cancer survivors.

Many of the pain syndromes described to date in cancer survivors share in common iatrogenic nerve injury with a resulting neuropathic pain syndrome.[23,24] The following paragraphs will therefore concentrate on current recommendations for neuropathic pain. It should be noted that survivors may experience other kinds of pain as well, and readers are referred to current texts for further discussion.[25–27]

5.0. APPROACH TO NEUROPATHIC PAIN

There is a wide range of choices in the approach to treatment of neuropathic pain. Potential treatments range from noninvasive measures, such as transcutaneous electrical nerve stimulation (TENS), physical therapy, to pharmacotherapy, to neurosurgical interventions in refractory cases.[28]

Pharmacologic interventions include tricyclic antidepressants, anticonvulsants, and anesthetic agents. Sequential single drug trials are recommended, with the drug dose escalated to the maximal allowable dose, before proceeding to the next agent. Various algorithms have been proposed. One general approach includes the use of opioids for severe pain, anticonvulsants for spontaneous or lancinating pains, and

Table 1. General Interventions for Neuropathic Pain

Medication	Level of evidence
Gabapentin, 5% lidocaine patch, opioid analgesics, tramadol, tricyclic antidepressants	More than one RCT (Ia)
Lamotrigine, carbamazepine, venlafaxine, bupropion, citalopram, paroxetine	At least one RCT (Ib)
Other second-generation anticonvulsants (levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide), capsaicin, clonidine, dextromethorphan, mexiletine.	(At least one well done study) Level IIa

tricyclic antidepressants or gabapentin for other features of neuropathic pain such as burning, dysesthesias, or allodynia.[29] Reviews of older trials provide estimates for the number needed to treat (NNT) for tricyclic antidepressants (NNT 2–3), opioids (NNT 2.5), and anticonvulsants such as gabapentin (NNT 3.8). Based upon this, one might consider topical lidocaine patches for patients with post-herpetic neuralgia, and then alternate trials of tricyclic antidepressants or serotonin reuptake inhibitors for patients with other neuropathic pain syndromes before proceeding to opioids.[30] Most of the evidence cited is derived from trials in patients with post-herpetic neuralgia or diabetic neuropathy. Consensus recommendations for the treatment of neuropathic pain are presented in Table 1.[31] Further work is needed in larger trials with head to head comparisons.

6.0. PAIN SYNDROMES SECONDARY TO TREATMENT FOR CANCER

6.1. Surgery

(i) Post surgical pain syndromes are now recognized as a distinct clinical entity with an overall incidence of 1–2%.[32] In addition to the syndromes mentioned in this chapter, these include syndromes of post-Coronary Artery Bypass Graft pain, post-sternotomy pain,[33] and post-herniorrhaphy pain.[34] During surgery, nociceptive stimulation leads to a barrage of C fiber impulses that activate spinal cord receptors and result in the development of central sensitization and a clinical hyperalgesic state.[35]

There have been few randomized clinical trials in this area. In the largest such trial to date, 99 patients with neuropathic pain resulting from mastectomy, thoracotomy or nephrectomy, were randomized to capsaicin (0.075%) for 8 weeks followed by placebo, or placebo followed by capsaicin. The study cream was placed over the painful area. The patients who started with capsaicin had more skin burning but subsequently reported pain reduction of 53% compared to 17% in patients who did not get capsaicin.[36]

(ii) Phantom pain is defined as pain referred to a surgically removed limb or a portion thereof.[37] Traditionally associated with limbs, phantom pain has been reported for resected internal organs such as the stomach, rectum, uterus, and bladder.[38] Phantom pain should be differentiated from stump pain and phantom sensations. Phantom pain sensations may vary considerably over time.[39] Worsening phantom limb pain after a period of stable pain should raise suspicion for a new malignancy.[40–42]

Data are limited on the appropriate management of patients with phantom pain. A large variety of treatments have been studied in small number of patients with few findings.[43] The goal of treatment is to control both the peripheral painful stimulus and the cortical reorganization which accompany phantom pain. There has been much interest in nonmedical approaches such as transcutaneous electrical nerve stimulation (TENS), hypnosis and acupuncture with limited data. Regarding medical treatments, small randomized clinical trials have found analgesic effects for morphine 70 mg to 200 mg orally,[44] and gabapentin for up to 2400 mg daily at 6 weeks.[45] A small crossover trial found that dextromethorphan 60 or 90 mg orally twice a day decreased pain intensity by greater than 50%.[46] Ketamine boluses increased pressure pain thresholds and reduced wind up pain.[47] Mirrors can induce analgesia.[48] A randomized trial of amitriptyline up to 125 mg daily did not show any effect.[49] Currently, patients with phantom pain should be approached in the same way as other patients with neuropathic pain syndromes until a better evidence base is developed.[50,51]

6.2. Radiation Therapy

(i) Brachial plexopathy: This condition has been seen more frequently in patients with breast cancer, and some patients with lung cancer and Hodgkin's lymphoma.

Risk factors for plexopathy in breast cancer patients include larger doses of radiation, radiation technique, and administration of chemotherapy. A key feature is delayed onset. Most patients present at a median of 1.5 years after treatment. In one larger study of 150 patients, long-term effects and onset of symptoms could present at 30 years after radiation.[52] In another study of women who had received radiation to the supraclavicular lymph nodes, median time to onset of brachial plexopathy was 88 months and the incidence did not decrease over time.[53] As radiation delivery becomes more precise, the incidence of this complication should decrease in the future.

Patients' complain of causalgia and weakness in the arm and shoulder, followed by chronic pain and progressive weakness. Milder forms may resolve spontaneously, but for many patients, pain is chronic and severe, and may be accompanied by motor deficits. The finding of myokymia on EMG studies may help in making a diagnosis of radiation induced brachial plexopathy. The syndrome may be difficult to distinguish from recurrent tumor or radiation induced malignancy even with MRI imaging. Published experience with PET scans is limited.[54]

Data on treatment are sparse. In one series of 33 patients, morphine was effective and given long term for 17 patients, and 3 patients improved with chemical sympathectomy.[55] Surgical interventions have generally not been successful,[56] although there have been successful case reports of neurolysis and Dorsal Root Entry Zone lesions in patients.[57,58] A randomized trial of hyperbaric oxygen versus placebo did not show any difference.[59] Nonpharmacological methods, such as occupational therapy, can be helpful for patients.[60]

(ii) Radiation lumbosacral plexopathy: Lumbosacral plexopathy has been reported in patients who received radiation for prostate or gynecological cancer, and is thought to occur rarely. In a retrospective study, the median time to onset of symptoms was 5 years, with a range of 1 to 30 years. The differential diagnosis is recurrence of cancer. Patients with radiation lumbosacral plexopathy may present with bilateral weakness followed by mild to moderate pain whereas patients with tumor recurrence may present first with unilateral, often severe pain followed by weakness.[61,62] No specific treatments have been reported for this syndrome.

(iii) Pain with movement in patients with fibrosis: In a review of 152 patients with limb sarcoma who had received limb sparing surgery followed by radiation therapy at the National Cancer Institute from 1975 to 1986, with a mean follow-up of 7 years, pain requiring opioids was reported by 10 patients (7%), and was associated with a high Nominal Standard Dose, as was edema, decreased range of motion, decreased manual muscle strength, and skin telangiectasia.[63]

(iv) Pelvic pain: Pelvic insufficiency fracture of the sacrum or pubis can occur in women who have received radiation therapy for pelvic malignancies with an actuarial incidence over 5 years estimated at 2.1%.[64] This syndrome presents as new pain in the sacroiliac joints and pubis in a previously radiated field, and may be mistaken for metastases. CT scan shows fractures[65] and further workup is not indicated. The pain usually responds to NSAIDs. While it is most well described in patients with gynecological malignancies, this syndrome has also been reported in patients with other indications for pelvic radiation, such as prostate cancer and rectal cancer.

6.3. Chemotherapy

Long-term studies have suggested that survivors who received chemotherapy as adjuvant therapy have decreased physical functioning compared to survivors who received other forms of local therapy. Interaction between treatment and diagnosis was found for aches and pains in one study of breast and lymphoma survivors, and lymphoma patients who received chemotherapy had the lowest quality of life. The authors speculated that enduring side effects of chemotherapy could affect physical aspects of quality of life.[66] In another study of breast cancer survivors, past chemotherapy was associated with poorer quality of life.[67] Chemotherapy-related pain could be an explanatory variable.

Chemotherapy-related peripheral neuropathy has been reported for a number of chemotherapy agents, including vinca alkaloids[68] (lymphoma and Acute lymphocytic leukemia patients), paclitaxel,[69] docetaxel[70] (ovarian cancer, lung cancer, breast cancer), cis-platin (germ cell tumor, lung cancer, ovarian cancer, head and neck cancer, colon cancer, lymphoma), oxaliplatin[71] (gastrointestinal malignancy), thalidomide[72] (hematological malignancy, GVHD), and bortezomib (multiple myeloma, myelodysplastic syndromes).

Multiple studies have been performed to study preventive measures. There are no specific recommendations for management of chemotherapy-related neuropathy.[73,74]

6.4. Hormonal Therapy

Patients with prostate and breast cancer are at increased risk for osteoporosis-associated fracture because of hormonal and other forms of cancer therapy.[75] In recent reports, prostate cancer patients have a 19% incidence of fracture after androgen deprivation, compared to 12% in patients who did not receive androgen deprivation.[76] In another large study, the relative risk of hip fracture for men who underwent orchiectomy was 2.11 (95% CI: 1.97–2.36), with the increase seen after orchiectomy and persisting for at least 15 years.[77] These findings are higher than earlier findings of a 9% fracture incidence in patients treated with LHRH agonists.[78]

Data from the Women's Health Initiative Observational Study show that the marrow density in breast cancer survivors is decreased compared to age-matched controls because of decreased use of hormonal therapy, but the rate of bone loss and of underdiagnosis is similar for both survivors and controls.[79] Patients with a diagnosis before the age of 55 are at increased risk for fracture (Hazard ratio 1.78, 95% CI: 1.28–2.46), and the overall risk of fracture for all survivors is 1.15(95% CI: 1.05–1.25).[80]

6.5. Supportive Care

Bisphosphonates—A small percentage of patients who receive bisphosphonates can develop osteonecrosis of the jaw after undergoing dental procedures.[81]

6.6. Transplantation

In a quality of life survey of 125 adults with hematologic malignancies who had survived for a median of 10 years (range 6–18) after bone marrow transplantation, a number of physical symptoms were reported, including fatigue (56%), eye problems (49%), sleep disturbance (43%), general pain (43%), joint/muscle pain (38%), constipation (27%), diarrhea (22%), and nausea/vomiting (13%). The intensity of these symptoms was mild. However, there was a small group of six patients who experienced significant pain and other symptoms from complications of graft versus host disease (GVHD).[82]

More information on pain and symptoms comes from a longitudinal study of 415 patients who completed a battery of quality of life instruments, including the EORTC QLQ-C30 and a Bone Marrow Transplantation Module, on an annual basis for 5 years. Extensive GVHD was experienced by patients in the first and second years after transplantation. One finding was that symptom patterns depended on the underlying diagnosis. Patients with acute leukemia, chronic leukemia, breast cancer, and non-Hodgkin's lymphoma had mild but stable levels of pain (22 out of 100 point scale) whereas patients with other diagnosis experienced a decrease in pain over time. Scores for overall pain in joints, and muscle pain in the Transplantation module increased over time for breast cancer patients but not for patients with other diagnoses.[83]

Graft versus host disease: Patients with chronic graft versus host disease may experience eye pain from keratoconjunctivitis, mouth pain from oral mucositis, abdominal pain from colonic GVHD, and bone pain from avascular necrosis.[84]

In a quality of life survey with the EORTC QLQ-C30 of patients with hematologic malignancies at 1 year follow-up who had received allogeneic stem cell transplant, autologous transplant, or combination chemotherapy, the allogeneic group differed from the combination chemotherapy group for items of pain and sleep disturbance.[85]

7.0. PAIN SYNDROMES BY PRIMARY SITE

7.1. Head and Neck Cancer

7.1.1. *Epidemiology*

Surveys have been done in convenience samples and in patients with specific malignancies. In a survey of 71 survivors 3 years out, participants completed the University of Washington Quality of Life Scale[86] and other quality of life instruments. The most common cancer sites were the larynx, oral cavity, oropharynx, and hypopharynx. Patients who underwent combined surgery and radiation had significantly worse scores for pain than patient treated with radiation or surgery alone ($p < 0.01$) Patients who experienced pain or disfigurement were more likely (RR 2.18, $p < 0.05$) to have concerns about cancer recurrence.[87] In another survey of 135 survivors 3 years out who completed the SF-36[88] and the EORTC QLQ C H&N 35,[89] patient data was compared to population norms. The most common tumor sites were the oral cavity (40 patients), pharynx (35 patients), and larynx (28 patients). Overall SF-36 bodily pain was similar for the two groups. However, the cancer survivors were significantly worse compared to the population for the H&N35 scales for local pain, swallowing, senses, and social eating.[90]

In a study of 182 patients with nasopharyngeal carcinoma who had lived for more than 2 years, responses to the Chinese version of the SF-36[91] were compared to 182 age-matched controls who did not have cancer. Half of the patients had been treated with conformal therapy, 18% received concurrent chemotherapy, and the median survival was 6 years. There was no difference in the frequency of bodily pain between the survivors and population controls, although functional domains were impaired for survivors.[92]

In a survey of 113 patients who had been treated for oropharyngeal carcinoma, no difference in pain or other symptoms, as measured by the EORTC QLQ-C30 H&N35 symptom scale score, was seen between patients who had received surgery plus RT(27) to treatment with radiation,[86] T stage, localization of tumor, or time from treatment to quality of life evaluation. Patients with T4 disease and who had developed second primary cancers were excluded, and median follow-up was 62 months. The sample represented 73% of the initial cohort.[93]

7.1.2. Pain Syndromes

Post-radical neck dissection syndrome is defined as neck and/or shoulder pain starting within 2 months after radical neck dissection. Patients complain of sharp or shooting pains in the ear, neck, and shoulder. The prevalence of this syndrome is unknown. In one survey of 25 patients with this diagnosis, all had neuropathic pains in the distribution of the superficial cervical plexus and 72% experienced regional myofascial pain.[94] There are no specific recommendations. Carbamazepine has been recommended because of its effectiveness in a related condition, trigeminal neuralgia. A pilot trial of botulinum toxin A in 16 patients decreased pain severity.[95]

Head and neck cancer survivors are at increased risk for myofascial pain syndromes, which may respond to relaxants such as cyclobenzaprine.

7.2. Breast Cancer

Breast cancer survivors may experience breast pain, arm pain, and dyspareunia. The breast pain often results from surgery, the arm pain is secondary to lymphedema, and dyspareunia is considered a menopausal symptom related to hormonal therapy.

7.2.1. Epidemiology

In a study of 55 of 111 eligible patients 2.7 years after surgery, 60% reported pain.[96]

The effects of adjuvant therapy are illustrated by a study of 817 patients with stage I or stage II breast cancer who had been followed for an average of 6.3 years. The patients completed the SF-36 and other instruments. Changes in bodily pain were statistically but not clinically significant, and there was no change in the incidence of dyspareunia. When compared by adjuvant treatment, differences in the domain of bodily pain were seen, with the lowest score for patients on tamoxifen alone, and the highest for patients who did not receive tamoxifen or chemotherapy.[67]

Prevalence may also differ by ethnic groups. In a study of 116 multiethnic urban women in an urban area who had undergone breast cancer surgery, the overall prevalence of pain attributed to cancer treatment was 79%. Rates were increased for African Americans (91%) and Latinas (93%) compared to Caucasians (54%), perhaps related to a more advanced disease stage and higher rates of mastectomy in the African American and Latina groups. The length of time from surgery was not reported.[97]

Patients after mastectomy may experience shoulder pain, phantom breast sensations, and otherwise unexplained sensations in addition to postmastectomy pain. In one study of Finnish hospitals, the prevalence of chronic pain ranged from 43% to 56%, strange sensations 26–45%, phantom breast sensation 26–66%.[98] Mastectomy–related symptoms are highlighted by a survey of 124 Quebec City survivors at 8 years after mastectomy. In comparison with a control group, survivors were more likely to report arm problems, defined weakness, stiffness, pain, swelling, loss of sensation, and limited range of movement (64% vs. 43%, $p < 0.04$).[99]

7.2.2. Pain Syndromes

A classification of pain syndromes includes phantom breast pain, intercostobrachial neuralgia (or postmastectomy pain syndrome), neuroma (scar) pain, and pain from other nerve injury.[100]

7.2.2.a. Phantom Breast. Phantom breast syndrome is the sensation of a breast after mastectomy, and can include nonpainful sensations as well as phantom breast pain. Phantom breast sensations can start more than 1 year after the mastectomy. In a prospective study of 120 women over 1 year, the incidence of phantom breast syndrome was 26% and phantom breast pain was 13% at 3 weeks postoperatively and similarly at 1 year follow-up. Painful scars were reported by 35% at 3 weeks and 23% at 1 year. The incidence of phantom breast syndrome was greatest in patients less than 50 years old.[101]

7.2.2.b. Postmastectomy Pain Syndrome (PMPS). In this syndrome, pain commences immediately or soon after any type of breast cancer surgery including mastectomy or removal of a lump. The pain affects the anterior thorax, axilla, and/or medial upper arm,[102] and is typically described as shooting, aching or burning. Postmastectomy pain can also be experienced by women who have undergone only lumpectomy without axillary dissection and with sparing of the intercostobrachial nerve.[103]

Estimates of the prevalence of PMPS range from 20% to 50%. In one study of 134 breast cancer survivors, 48% of the total sample reported pain and 27% reported postmastectomy pain. Patients who had undergone lumpectomy and radiation were as likely to report postmastectomy pain. Approximately, one third of pain patients associated the pain to the presence of disease recurrence. Interestingly, of the patients who reported mastectomy pain, eight were evaluated at a Pain Management Center, where the diagnosis was verified.[104]

More information comes from a survey of 408 women who underwent mastectomy between 1990 and 1995 in Scotland, where 175 women (43%) reported postmastectomy pain in 1996 with a median follow-up of 3 years. Prevalence was increased in younger women.[105] In a follow-up study at 9 years from surgery of 138 survivors reporting pain, with responses from 113 (82%), half of the patients reported resolution of their postmastectomy pain syndrome. Patients with persistent pain had significantly decreased quality of life compared to those whose pain had resolved.[106]

7.2.2.c. Treatment. There have been few trials in this area. Amitriptyline in a dose range of 20–100 mg was effective in a small randomized crossover trial.[107] In another small randomized crossover study of 13 patients, venlafaxine titrated from 18.75 mg to 75 mg daily produced greater pain relief than placebo although average pain was the same.[108] Topical capsaicin at a strength of 0.025% has been effective in small single arm trials.[109,110]

Many patients resort to nonpharmacologic measures for pain relief. Trials of combination of opioids and adjuvant analgesics (multimodality therapy) may be sufficient to control postsurgical pain syndromes.

7.2.3. Measures to Prevent Postmastectomy Pain

The effect of special attention to preserving the intercostobrachial nerve was studied in a group of 120 patients, who were randomized to either sacrifice or preservation of the nerve. The number of patients who experienced pain, numbness, and altered sensation was halved in the preservation group postoperatively but not at follow-up 3 months later.[111]

The role of axillary dissection is highlighted by a study comparing 85 patients who underwent axillary dissection to 65 patients who had sentinel node dissection. Patients with sentinel node dissection showed significantly better scores for pain, edema, and range of motion as measured with a symptom disability summation score.[112]

A possible role for postoperative pain management is suggested by one study of 110 breast cancer patients who were interviewed 3–4 years after breast surgery. Twenty-eight patients (25%) reported chronic pain. Of these, 21 (75%) had received conventional postoperative analgesia whereas 53% of the original cohort had received conventional analgesia.[113]

Following the model of preemptive pain management, a randomized trial of perioperative venlafaxine vs. placebo showed significant reduction in the incidence of chest wall pain, arm pain, and axilla pain between the treatment and control groups at 6 months after the surgery.[114]

Other interesting determinants of pain were suggested from telephone surveys of a national sample of 1812 Medicare beneficiaries who had been treated up to 5 years previously for early stage breast cancer. Axillary dissection was a predictor for arm problems, which in turn affected quality of life. Having a choice in treatment was associated with less bodily pain, implying that processes of care may affect perceptions of pain.[115]

7.2.3.a. Lymphedema. Lymphedema refers to swelling in an extremity, and is associated with painful sensations of swelling, heaviness, aching, tenderness, and numbness. These symptoms may be mild and not volunteered to health care professionals. In one review, the incidence of lymphedema in breast cancer patients ranged from 6% to 30%.[116] In a cohort of 263 breast cancer survivors who had undergone axillary dissection 20 years previously, 128 patients (49%) reported a sensation of swelling, and 33 patients (13%) had severe lymphedema, defined as a difference in arm circumference of greater than 2 cm. While 98 patients (77%) developed within the first 3 years of diagnosis, onset could occur up to 17 years later.[117] The incidence of lymphedema may decrease in the future as axillary dissections become more limited, and radiation techniques advance. In a telephone survey of 148 breast cancer survivors, 15% reported moderate to severe pain, and pain severity and swelling explained 25% of the variance in arm function.[118] Pain from lymphedema can cause significant psychological distress.[119, 120]

7.2.3.b. Treatment. A randomized comparison of manual lymphatic drainage to simple lymphatic drainage in 31 patients found a reduction in pain in patients who had manual lymphatic drainage, as well as other symptoms and quality of life parameters.[121] Benzopyrones have been an area of interest. A large randomized study of 140 women compared either coumarin 200 mg or placebo twice a day for 6 months and did not find any effect on arm volume or symptoms.[122] A Cochrane Database review concluded that the current evidence available is too weak to draw any conclusions.[123]

7.3. Lung Cancer

7.3.1. Epidemiology

In a survey of 57 lung cancer survivors, 56% had frequent pain, 46% had chronic pain from scars and surgery; 25% had pain not controlled by medication.[124]

7.3.2. Pain Syndrome

7.3.2.a. Post thoracotomy pain syndrome. In this syndrome, pain recurs or persists along a throracotomy scar at least 2 months following the surgical procedure.[125] The prevalence varies. It has been estimated that 50% of patients who undergo thoracotomy will have mild to moderate pain and 5% of patients will have severe post thoracotomy pain.[126] Pain at postoperative day 1 is predictive of pain 1 month and 1 year after thoracotomy.[127] Physical exam usually shows sensory abnormalities such as absence of sensation or allodynia. Tumor recurrence should be excluded if the character of the pain changes, or becomes increasingly severe. Earlier reviews found little evidence for effective interventions.[128] Capsaicin was effective in a trial for surgical neuropathic pain (see above),[36] and topiramate was active in a small series of patients.[129] This remains a difficult problem.[130]

One group compared transdermal nitroglycerin to transdermal nitroglycerin 5 mg/day with etodolac in an open label trial in patients with etodolac insensitive pain. These workers found an improvement in VAS pain severity, breakthrough pain, and sleep efficiency at on day 14 of treatment.[131]

Interest in preventing post thoracotomy pain has led to a comparison of video-assisted thoracoscopy (VATS) with thoracotomy. In the largest study to date, with a median follow-up of 36 months, 27 VATS and 24 thoracotomy survivors completed a telephone survey with the EORTC QLQ-C30, LC-13 and a chest pain subscale. No difference was found between the two arms for any of the pain items. Only one third of the original pool was able to participate in the study because of other medical conditions, illustrating the difficulty of recruiting patients.[132] An extensive body of work has been done and is ongoing regarding the use of perioperative epidural analgesia. Findings have shown some improvement in postoperative pain, and conflicting results regarding chronic pain.

7.4. Colon Cancer

7.4.1. Epidemiology

In a survey of 117 colon cancer survivors, 30% frequently experienced pain. In another community-based survey, 173 colorectal cancer survivors completed a quality of life instrument, the FACT-C,[133] and the Health Utilities Index-Mark III.[134] These researchers found that pain did not improve over time. Lower income status was associated with the pain dimension on the HUI and the physical dimension of the FACT-C. More detailed information regarding pain was not available.[135] In a survey of 259 long-term (mean follow-up 9 years) female colorectal cancer survivors who completed the SF-36, bodily pain scores varied with the number of comorbid conditions with a correlation coefficient $r = -0.42$, $p < 0.001$. The comorbid conditions included arthritis (57%), hypertension (46%), anxiety (19%), and osteoporosis (18%).[136]

Phantom pain has been regularly reported. In one group of 40 survivors, 26 (65%) experienced phantom rectal sensations, with onset in the postoperative period, to starting 8 years later. In six patients, the sensations had spontaneously stopped.[137] In a series of 22 survivors who had undergone abdominoperineal resection, 68% experienced a phantom rectum, and a smaller subset of 18% reported phantom pain with sensations of phantom pain like hemorrhoids, pricking and shooting, or like hard feces that would rupture the rectum. This started within 1–2 months after surgery, and the severity decreased over time.[138]

A perineal pain syndrome was described in a group of 286 patients with rectal cancer who underwent perineal resection, where 11% developed a chronic perineal pain syndrome. Patients with early onset pain had a 26% tumor recurrence rate and those who presented several months later had an 80% recurrence rate.[139] Patients with locally recurrent rectal cancer have a 40% chance of experiencing significant posttreatment pelvic pain.[140] In another follow-up study in 121 rectal cancer survivors with a median follow-up of 2 years, 20 patients (15%) reported persistent pain, and this significantly affected their quality of life.[141]

7.5. Hematologic Malignancies

7.5.1. Epidemiology

In the Childhood Cancer Survivors Study, 8.6% of patients with leukemia reported pain related to cancer or its treatment. In one study of 161 Acute Lymphocytic Leukemia survivors at a single institution, 30% reported pain. The presence of pain was a predictor for fatigue (OR = 5.56, 95% CI: 2.13–14.5) and for depression (OR = 5.04, 95% CI: 2.15–11.9).[142]

7.5.2. Pain Syndromes

Patients with a history of lymphomas may experience chemotherapy-related neuropathy from the use of vinca alkaloids, cisplatinum, and taxanes. They are also at increased risk for herpes zoster.

Patients with plasma cell dyscrasias experience painful sensory neuropathy, especially those with osteosclerotic myelomas, or cryoglobulinemias.[143] Painful neuropathies from the disease often improves but may not resolve once the underlying disease has been treated. Chemotherapy-related neuropathy from thalidomide or bortezomib may improve once the treatment has stopped, but may persist as well. (Also, see comments under stem cell transplantation.)

7.6. Testicular Cancer

7.6.1. Epidemiology

One survey of QOL in French testicular cancer survivors with a median survival of 11 years found no difference in scores for pain between patients and controls.[144] In a larger study of 1409 testicular cancer survivors with median 11 years of follow-up, survivors reported more bodily pain than controls, and this was statistically but not clinically ignificant. Approximately, 15% of patients reported peripheral sensory neuropathy, and 20% reported Raynaud's phenomenon. Patients who had received chemotherapy were more likely to report neuropathy or Raynaud's syndrome.[145] Another study of 277 survivors found that patients who reported Raynaud's (cold white fingers) were more likely to report leg pain ($p < 0.01$) and other constitutional symptoms.[146]

7.6.2. Pain Syndromes

Patients may experience phantom orchalgia, and are at risk for developing radiation-related plexopathy, chemotherapy-related neuropathy, and Raynaud's syndrome.

7.7. Prostate Cancer

7.7.1. Epidemiology

Very little has been reported on pain in prostate cancer survivors. Studies to date have focused on sexuality, other symptoms, and communication problems faced by prostate cancer survivors and their families.

7.7.2. Pain Syndromes

7.7.2.a. Post-prostatectomy pain. In a prospective survey of 110 patients who underwent radical retropubic prostatectomy, 50 patients reported pain 3 months later, experienced most commonly in the genitals, abdomen and incision site. At 6 months, 35% still had pain and it affected their perception of overall health, physical function, and social function.[147]

7.7.2.b. Prostate brachytherapy. A small series of three patients developed perineal pain worsened by standing after receiving brachytherapy.[148]

7.7.2.c. Prostate cryotherapy. In one series of 38 patients who underwent cryotherapy, 40% experienced rectal pain afterwards.[149]

7.8. GYN Cencers

7.8.1. Epidemiology

In one mail survey with responses from 200 ovarian cancer survivors, pain related to the cancer or its treatment was reported by 53.5%, and located primarily in the bowel, pelvis, bladder, or groin. Of women who had received radiation therapy, 34% reported painful intercourse or discomfort with bowel movements. Pain was severe in 21% of patients who reported pain.[150]

For cervical cancer survivors, a survey of 202 patients from a state registry found an incidence of depression in 21%. The mean pain intensity on a scale of zero to ten was 2.4 (SD = 2.7) for nondepressed patients and 4.3 (SD = 3.1) for depressed patients. Patients who reported moderate or severe pain were more likely to experience depressive symptoms (OR = 2.74; 95% CI: 1.61–4.65).[151] In another survey of 46 cervical cancer, survivors reported back pain (47%), leg pain (38%), and headache (36%) but there was no difference in prevalence compared to a control group.[152]

Patients who received radiation therapy have varying responses about pain. In a survey of 230 cervical and vaginal cancer patients who had been treated with curative intent radiation therapy, quality of life was assessed with the EORTC QLQ-C30. At 12, 18, and 24 months, patients had a lower pain scores than a control population.[20] Similar results were found in a group of 49 endometrial cancer survivors treated with radiation therapy.[153] In another survey of 94 survivors at 3–4 years after pelvic radiation therapy for endometrial and cervical cancer, patients with pain in the lower back and other parts of the body rated their quality of life lower in a site-specific module of the EORTC QLQ-C36. Their response to the general pain item suggested that these survivors experience less pain than a control group drawn from the general population. However, the authors suggest that survivors may have understood the two types of questions differently.[154]

7.8.2. Pain Syndromes

Patients with ovarian cancer often experience chemotherapy-related neuropathy from the administration of cisplatinum and taxanes as part of their treatment.

Lower limb lymphedema—In a survey of 487 women who had been treated for gynecologic malignancies, a diagnosis of lymphedema was made in 89 (18%), of which 82 were interviewed. Forty-nine patients (60%) experienced pain, and 13 (27%) more than one type of pain. Other descriptions included a feeling of fullness, an ache, tightness, sharp pain, and throbbing sensations. Issues of pain management were not addressed in this study, and subsumed under management with compression garments, physical therapy, changes in clothing, information received, and changes in body image. [155]

8.0. FUTURE RESEARCH

As this chapter highlights much remains to be learned about pain and pain treatment among cancer survivors. Some areas that seem promising include the following:

a. Descriptive epidemiology of the different kinds of pain syndromes, both treatment- and non-treatment-related, in cancer survivors. This will require the design of large scale surveys specifically designed for comprehensive pain assessment.[156]
b. Continued research into the classification and characterization of pain syndromes which affect cancer survivors, including identification of new pain syndromes that may emerge with new approaches to cancer.
c. Understanding the meaning of these syndromes to survivors, in the setting of other pain syndromes, and how these may affect their responses to survey questions.
d. Understanding of the pathophysiology underlying pain syndromes in cancer survivors, and their relationship to other symptoms, such as fatigue and depression.
e. Adequately powered RCTs of interventions in pain management in survivors of different cancers with longer term follow-up. These could include coping strategies for uncertainty caused by the presence of pain, and pharmacologic and nonpharmacologic interventions.
f. Encourage ongoing research on prevention of iatrogenic pain syndromes.
g. Research directed at understanding how pain affects the daily lives of cancer survivors (e.g., work) and how survivors cope with pain over time.
h. Education of both patients and health care providers about pain, and inclusion of pain management as an element of survivorship planning.

9.0. SUMMARY

The prevalence of pain and pain syndromes in cancer survivors varies by tumor type and therapy. When present, pain is often associated with decreased function and quality of life, as well as other symptoms. The taxonomy of pain syndromes in cancer survivors is incomplete. There are a number of very important questions regarding pain in cancer survivors that remain unanswered.

Patients who are younger, have lower socioeconomic status, and are within 5 years after primary cancer treatment are at greater risk for experiencing distressing pain syndromes.

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Chapter 10

Depression

Peter C. Trask and Timothy Pearman

1.0. INTRODUCTION

The focus of this chapter is on the presence of depression in cancer survivors. We will not focus on the related issues of anxiety (including posttraumatic stress disorders), or the broader concept of distress. We will also try to restrict our discussion to the occurrence of depression as a unitary construct, although we are fully aware that depression commonly co-occurs with pain and fatigue, as well as the aforementioned psychiatric conditions. The definition of depression that we will use will be outlined in the pages that follow, but to the extent possible, whenever researchers have not used clinical interviews to determine depression, this will be noted.

2.0. DEFINITION OF CANCER SURVIVOR

Depending on whom you speak with, one is likely to get different definitions of who qualifies as a cancer survivor. According to individuals who study long-term effects of cancer treatment, a cancer survivor is someone who has completed therapy at least 5 years ago and has no signs of cancer. Others, however, notably the National Coalition for Cancer Survivorship (NCCS: www.canceradvocacy.org), state that one becomes a cancer survivor the day they are diagnosed. If this definition is used, then there are clear "seasons of survival" that an individual with cancer goes through, including adjusting to the diagnosis, surviving treatment, returning to a normal life, and long-term, posttreatment adjustment.

In this chapter, we agree with the NCCS and define one as a survivor from the day of his or her diagnosis. Using this definition allows us to discuss the issue of depression at the point of cancer diagnosis, during cancer treatment, and after cancer treatment (both shortly after and following a longer period).

One reason for this focus on the individual from the point of diagnosis is that depression can occur at any time, and cancer patients as a group have not identified one point along the cancer trajectory as being the most stressful. To illustrate, Northouse *et al.*[1] reported that 39% of women found the initial diagnosis as most stressful, but 51% found the time of recurrence as most stressful, while 10% noted both times as equally stressful. Given this variability in the time when depression can potentially occur, it is important to present a summary of the research that has examined depression in cancer survivors from the point of diagnosis. Before presenting this information, it is necessary to first present a definition of depression, as well as an overview of how it has been assessed in the individual with cancer.

3.0. DEFINITION OF DEPRESSION

Depression is defined through the DSM-IV as the presence of depressed mood or loss of interest or pleasure in nearly all activities for a period of at least 2 weeks.[2] The individual must also have four of the additional symptoms presented in Table 1. They include symptoms that can be conceptualized as encompassing somatic (e.g., weight/appetite, fatigue) and cognitive (e.g., poor concentration, guilt) changes from normal functioning that result in significant distress or impairment.

3.1. Diagnostic Issues

The diagnosis of depression in cancer survivors is difficult because symptoms of depression are often similar to those of the specific cancer or its' treatments. Treatments for cancer (e.g., radiation, chemotherapy, biological therapy) often result in many of the symptoms needed for a diagnosis of depression such as fatigue, weight loss, anhedonia, cognitive changes, and psychomotor retardation. As such, it is difficult to determine with reasonable accuracy the source of these symptoms. In an attempt to identify an accurate method of assessing depression in medical patients and cancer patients in particular, researchers have employed four different approaches: inclusive, etiologic, substitutive, and exclusive.[3,4] These approaches are summarized in Table 2 and vary in the degree that they include symptoms that may be caused by a physical illness in the diagnosis of depression. The advantages and disadvantages of these approaches have been discussed in a previous paper by Trask[5] and will not be discussed in great detail here. The upshot, however, is that prevalence of depression can vary significantly in the same group of cancer survivors depending on which approach is used to diagnose depression. Moreover, different approaches have been used in different studies to examine the prevalence of depression in cancer survivors making it difficult to compare prevalence rates with any degree of certainty.

Table 1. DSM-IV Symptoms of Depression

Depressed mood*
Anhedonia*
Insomnia/hypersomnia
Fatigue/loss of energy
Significant weight/appetite change (increase or decrease)
Psychomotor agitation/retardation
Worthlessness/guilt
Reduced concentration, ability to think, or indecisiveness
Recurrent thoughts of death or suicide

*Either of these must be present for a diagnosis of major depressive episode by the DSM-IV criteria.

Table 2. Criteria for Depression by Each Diagnostic Approach

	Approach			
Symptoms	*Inclusive*	*Etiologic*	*Substitutive*	*Exclusive*
General				
Depressed mood	X	X	X	X
Anhedonia	X	X	X	X
Physical				
In/hypersomnia	X	X	X	X
Weight/appetite change	X	X		
Psychomotor agitation/retardation	X	X	X	X
Fatigue/loss of energy	X	X		
Psychological				
Worthlessness/guilt	X	X	X	X
Poor concentration/indecisiveness	X	X	X	X
Suicidal ideation/thoughts of death	X	X	X	X
Brooding			X	
Indecision			X	

Notes Etiologic differs from Inclusive in that it requires that a symptom count only if it is clearly not due to a physical condition.

Identifying an approach that could be employed quickly, accurately, and consistently across studies, time, or phases of survivorship would help in reducing the discrepancies and arriving at a realistic approximation of the prevalence of depression in cancer survivors.

4.0. ASSESSMENT APPROACHES AND ISSUES

Depression has been assessed using a variety of approaches including self-report, brief screening measures, and structured clinical interviews. Common self-report measures include the Hospital Anxiety and Depression Scale (HADS),[6] the Rotterdam Symptom Checklist (RSCL),[7] the Beck Depression Inventory (BDI: regular and short forms),[8,9] the Brief Symptom Inventory-Depression scale (BSI-D),[10–12] Center for Epidemiologic Studies Depression Scale (CES-D),[13] and the Zung Self-Rating Depression Scale (ZSRDS: both full and brief forms).[14,15] A major limitation of self-report measures is that they are unable to provide a diagnosis of depression, providing instead information as to the severity of depressive symptoms. An additional limitation is that the measures often include physical symptoms that may be the result of the cancer itself (e.g., feeling fatigued), and not feelings of depression.

In contrast, clinical interviews are strictly designed to provide a diagnosis of depression and other psychiatric illnesses. Indeed, structured clinical interviews have traditionally been considered the gold standard for identifying the prevalence, clinical significance, and potential treatment of depression because of their rigorous criteria. Common interviews include the Schedule for Affective Disorders and Schizophrenia (SADS),[16] Structured Clinical Interview for DSM (SCID),[17] Research Diagnostic Criteria (RDC),[18] and the Diagnostic Interview Schedule (DIS).[19] In addition, researchers and clinicians have used unstructured clinical interviews in which they diagnose depression based on DSM[20,21] or Endicott[22] criteria. Unfortunately, clinical interviews are not without limitations. Structured clinical interviews have been criticized for the length of time they take to administer and the amount of training that they require for proficiency in administration and scoring,[23] as well as having little reliance on contextual information. Semistructured interviews presumably would allow the interviewer to ask additional questions that would help determine whether the physical symptoms endorsed are the result of cancer or its treatment, are the result of another physical malady, or are indeed the consequence of depression. Perhaps a greater limitation of structured clinical interviews, however, is the fact that they were developed and validated on a population devoid of significant comorbid medical illness. The result, as Hall *et al.*[24] point out, is that even clinical interviews are unlikely to be completely reliable. Nevertheless, as previously mentioned, they are standard for diagnosing depression.

Having reviewed the basics of diagnosis and assessment of depression in cancer survivors, we will now turn to incidence, prevalence, and correlates of depression. Specifically, the remainder of this chapter will cover five areas. First, we will address the incidence of depression from the time of diagnosis through the end of primary treatment for cancer. Second, we will examine the research investigating the prevalence and correlates of depression after primary treatment. Third, we will provide an overview of studies of depression in long-term survivors of cancer. Fourth, we will briefly touch on psychosocial and biological theories of depression in cancer survivors. Finally, we will touch on directions for future research.

5.0. DEPRESSION AT DIAGNOSIS

There are very few articles that have assessed depression at the time of diagnosis of cancer. In contrast, there are several articles that have assessed individuals either between diagnosis and treatment, or following the initial surgery, but prior to the beginning of adjuvant chemotherapy or radiation. As a result of this variability, for the purposes of this section, "at diagnosis" will be broadly defined as that period between an awareness of the cancer diagnosis and the beginning of treatment.

Over the past 20 years, the prevalence of depression at diagnosis has been examined using clinical interviews in a variety of cancer types including cervical, endometrial, vaginal, and breast. In an early study by Evans and colleagues,[25] depression was studied in 83 women with cervical, endometrial, or vaginal cancer who were admitted to a gynecological tumor service for cancer staging and initial treatment following a recent diagnosis. Except for 15 women who were hospitalized for a recurrence workup, all women had been diagnosed within approximately 2 months of admission. During hospitalization, each woman was evaluated by a psychiatrist using DSM-III diagnostic criteria. Major depression was identified in 23% ($n = 19$) women, and nonmajor depression was present in 24% ($n = 20$) (nonmajor depression included adjustment disorder with depressed mood, dysthymic disorder, adjustment disorder with mixed emotional features, and uncomplicated bereavement). Five years later, similar results were observed by the same investigators.[26] Specifically, 15 women (23%) who were being evaluated by a psychiatrist using DSM-III criteria during the first week of evaluation for cancer staging and initial cancer treatment or recurrence evaluation for cervical, endometrial, or vaginal cancer met criteria for major depression. Neither stage of cancer, nor the presence of a cancer recurrence differentiated depressed from nondepressed patients.

More recently, Keller *et al.*[27] assessed recently diagnosed individuals with colorectal, gastric, pancreatic, soft tissue, and other cancer diagnoses within a few days of admission to the hospital prior to undergoing surgery. Using the SCID for DSM-IV, out of 78 patients who were interviewed, major depression was diagnosed in 4 patients (5%), with adjustment disorder being diagnosed in another 17 (22%): 3 of those had depressed affect, whereas anxiety or mixed mood was prevalent in the remaining 14. The authors noted that the prevalence rates observed in their study were consistent with those seen across various oncologic settings, confirming the assumption regarding the vulnerability of patients undergoing surgery for either recently diagnosed or recurrent cancer. Interestingly, the prevalence of depression in their study is lower than that observed in the sample of individuals with gynecological cancer.

Finally, a study of 222 women under 60 years of age with a diagnosis of early breast cancer utilized the SCID to assess the presence of depression. The SCID specifically inquired about the presence of depression in the period from 1 month before their cancer diagnosis to 5 months following diagnosis.[28] DSM-III-R criteria were employed to classify women as a full case of depression, anxiety, or both, a borderline case or a non-case. The authors calculated the point prevalence as the percentage of women with depression, anxiety, or both in the month before this period, with the annual period prevalence being the percentage of women with at least one episode of depression, anxiety, or both over a 1-year period. The point prevalence of depression, anxiety, or both was 33% at diagnosis. The annual prevalences were 48% for the first year after diagnosis. They noted that previous psychological treatment was associated with depression, anxiety, or both around the period of diagnosis. Cancer treatment and tumor pathology was not associated with depression or anxiety. The duration of depression, anxiety, or both was at least 90 days in 40% of the women and less than 90 days in 20%. The remaining 40% of the women reported no episodes. Depression and anxiety were more prevalent after recurrence, with 45% of women (95% CI 28–64%) having an episode of depression, anxiety, or both in the 3 months after diagnosis of a recurrence and 36% of women (95% CI 30–43%) having an episode after the initial diagnosis. One problem with this study is that the authors reported only on the combination of depression, anxiety, or both instead of reporting the prevalence of each separately. As such, it is impossible to know whether anxiety was more prevalent than depression, vice versa, or that they occurred with equal prevalence.

Several studies have examined symptoms of depression as assessed by one of the previously identified patient self-report questionnaires. Nordin and Glimelius[29] investigated the ability to predict elevated levels of depression and anxiety 6 months after the diagnosis of gastrointestinal cancer in 159 patients. They asked patients to complete interviews as soon as their physical status permitted or within 12 weeks from the date of the diagnostic biopsy or primary surgery. Individuals were subsequently interviewed after 6 months. The HADS was used as a measure of depression with a score of 11 or more qualifying as a "case" of depression. They found that for HADS depression 6 months after diagnosis, 31% of the variance was explained by depression close to the diagnosis. Interestingly, only 24 individuals (21%) were identified as either "doubtful cases" or "cases" on the HADS at diagnosis (no breakout was provided for depressed versus anxious individuals).

In a more recent study to utilize the HADS, Iconomou *et al.*[30] assessed male and female chemotherapy naïve outpatients who had a solid malignancy diagnosis and were scheduled to begin adjuvant or first-line systemic chemotherapy. A score above 11 on the HADS qualified as a case. Eighty individuals were assessed at two separate occasions (before and after treatment). Twenty-five percent of the individuals had a

HADS depression score of 11 or greater at the baseline assessment with 29% of the individuals being depressed at the end of treatment.

Finally, Stommel *et al.*[31] studied a group of individuals 65 years of age or older who were enrolled in the study approximately 6 weeks after being newly diagnosed with breast, colon, lung, or prostate cancer. The initial interview was conducted 4–6 weeks after surgery or 2–4 weeks after the initial radiation or chemotherapy treatment. Additional interviews came after 2–3 months, 5–7 months, and 1 year from diagnosis. Depression was measured by the CES-D which has a range from 0–60, although nobody in the study had a score higher than 42. When the commonly used cutoff for depressive symptomology was used, 26.1% of the individuals at the first assessment were "depressed." This dropped to 15.8% by the last assessment a year later. As with several other studies, the assessment of depression at diagnosis in this study is combined with assessments that occurred following completion of some or all of the primary therapy.

The previous studies of depression at the time of diagnosis suggest that approximately 20–30% of cancer survivors will have diagnosable depression at the point of diagnosis. The consistent presence of depression surrounding the point of diagnosis and, as we will see shortly, continuing in many survivors through treatment strongly argues for both an assessment of depression at this point, as well as a system that will triage depressed patients to appropriate interventions.

6.0. DEPRESSION DURING TREATMENT

Several issues may contribute to the occurrence of depression in cancer survivors during treatment, including the age of the patient and the specific cancer therapy. Unlike the studies assessing depression at diagnosis, those assessing depression during treatment have relied primarily on patient's self-report and not clinical interviews. This is likely due to the increased time burden that clinical interviews place on patients at a time when the physical side effects may impair the individual's ability to focus for long periods of time. Unfortunately, several studies that have investigated depression in individuals during treatment have failed to provide the proportion of individuals with significant depression, reporting only mean scores instead. This is true in articles by Frost *et al.*[32] who assessed newly diagnosed women with breast cancer treated with adjuvant therapy, and Chen *et al.*[33] who assessed elderly cancer patients with the Geriatric Depression Scale. This same limitation was observed in an article on depression and pain in advanced hormone refractory prostate cancer patients receiving suramin and active therapy.[34] Despite that limitation, the study, which assessed individuals prior to therapy, during treatment, and then 3 months after the last dose, documents the decrease in depression scores from baseline to the middle of treatment. Unfortunately, depression subsequently increased at the 2-week posttreatment assessment, before reducing to almost baseline levels at the 3-month assessment. The study provides an example of the variability in depression scores that can occur during the course of treatment.

Additional information on the course of depression during treatment comes from an article examining individuals treated for melanoma with alpha-interferon.[35] In that study, Trask *et al.* assessed individuals for depression prior to initiating interferon therapy, after their high-dose treatment, and then at 1, 2, 3, and 6 months following high-dose treatment (during the time when they are treated with a lower maintenance dose) with the Brief Symptom Inventory and the BDI. Average scores

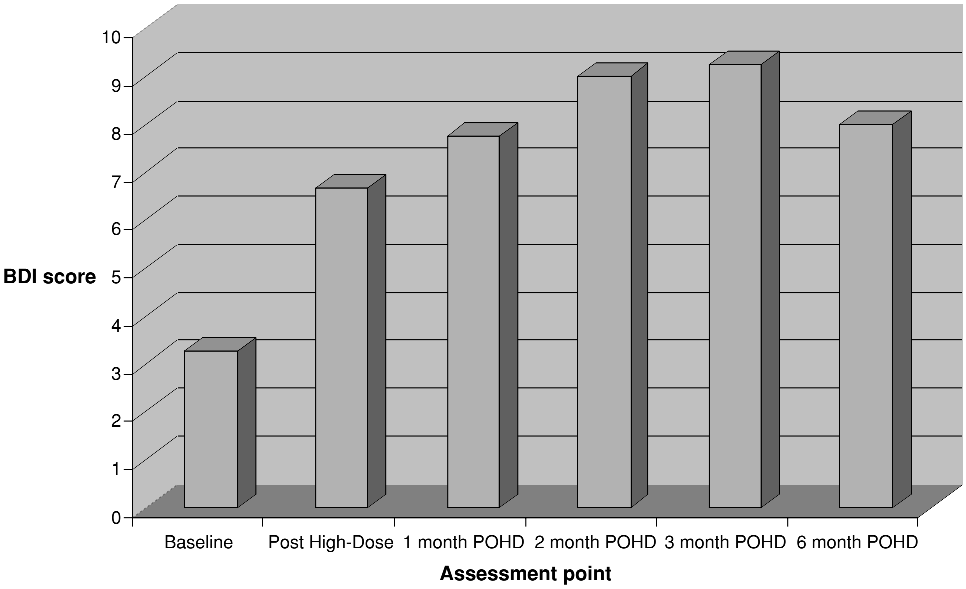

Figure 1. Changes in Depression in Individuals with Melanoma Over the Course of Interferon Therapy.

on both the BDI and the BSI-D increased from the first assessment through treatment and did not return to baseline levels by the 6-month assessment (see Figure 1) That said, at any measurement occasion only 17% met or exceeded the cutoffs for significant depression on either the BSI-D or BDI. Nevertheless, the results provide further evidence that cancer therapies can potentially cause symptoms of depression. Further research is needed to determine the mechanisms that may promote the development of depressive symptoms.

Epping-Jordan *et al.*[36] examined depressive symptoms in 80 women with newly diagnosed breast cancer. Women were assessed prior to treatment, with the majority ($n = 60$, 75%) also completing the study's initial assessment before undergoing any surgical procedure. Responses to the SCL-90-R indicated that at baseline, 34% of the sample had a depression T score above 63, suggestive of a clinical range of depressive symptoms. At 3- and 6-month follow-up (which occurred after most women had completed chemotherapy and/or radiation therapy), the percentage of women above 63 was 29% ($n = 23$) and 26% ($n = 21$), respectively. In this and the previous study, depression reduced as the time since diagnosis and treatment lengthened. Although one could conclude that depression may be self-limiting in some cancer survivors, for others, symptoms of depression continue even after the initial treatment has been completed. In the section that follows, the prevalence of depression in cancer survivors following treatment is reviewed along with the various issues that may impact (either positively or negatively) the development of depression.

7.0. DEPRESSION AFTER CANCER TREATMENT

Upon completion of treatment, individuals with cancer are typically expected to resume the responsibilities, activities, and roles of daily life. At the same time they begin to separate slowly from the close monitoring that they were receiving during their treatment from health care providers. The result is that cancer survivors routinely report that they face a new set of challenges upon completion of cancer treatment, with some likening the experience to "walking a tightrope without a net."

With this degree of uncertainty, cancer survivors who have completed treatment continue to be at risk for depression. The prevalence of depression in this population, however, has been historically understudied. As with the previous stages along the cancer continuum, assessment of the general prevalence of depression after treatment has been made difficult by the various assessment methods and time at which depression is measured following treatment. Generally speaking, the incidence of depression after cancer treatment is higher than that seen in the healthy population.[37] A number of risk factors for acute (i.e., before or during treatment) depression have been found, including diagnosis, gender, type of surgery, benefit finding, prior history of depression, and, of course, cancer prognosis.[38] Age has also been speculated upon as a possibly risk factor. Whether or not these risk factors continue to impact depression after treatment for cancer remains largely unknown. The sections that follow will further present the literature that has focused on the relationship between depression and the various risk factors.

Before progressing to the discussion of depression and correlates, however, several caveats should be made. Specifically, the following sections will cover only adaptation to active survivorship, as opposed to adaptation to palliative care. In general, studies have found that the incidence of depression in patients with advanced terminal cancer is similar to that found in a general cancer population.[39,40] In addition, the incidence of depression appears to be correlated with functional status and symptom intensity.[41] Finally, our discussion of depression will focus only on adults. This is in part because the challenges faced by children and their types of cancer are different than those faced by adults. In addition, most studies in the literature have found that children with cancer are no more likely to be depressed than healthy children and adolescents.[42]

8.0. CORRELATES OF DEPRESSION IN LONGER TERM SURVIVORS

A number of factors that correlate with depression after treatment have been described in the literature. These include cancer diagnosis, treatment type (chemotherapy, radiotherapy, surgery), age, prior history of depression, presence or absence of benefit finding, and coping style. In addition, the presence of depression in cancer survivors has been examined for its relation to mortality and morbidity. Readers are referred to Massie's review of this area,[38] which covers articles on depression and cancer through the year 2003.

8.1. Cancer Diagnosis and Depression

The majority of studies that have assessed depression in posttreatment cancer survivors have included in their sample individuals with disparate cancer diagnoses. As such, few studies exist in the literature examining the prevalence of depression in patients with a single cancer diagnosis. Several exceptions to this are studies that have focused on depression in breast cancer survivors. In one such study, longer term survivors of breast cancer had a clearly increased risk of depression (between 22 and 30%) compared to those with benign breast disease (less than 10%).[38] In another, Kornblith and Ligibel[37] pointed out that a significant subset of breast cancer survivors continue to experience significant depression and anxiety as long as 4 years posttreatment. They note that depression seems to be mediated in long-term survivors of breast cancer by ongoing medical sequelae, such as lymphedema.

In a study of 121 head and neck cancer survivors, Derks and colleagues[43] found that over the course of the year following treatment, the number of patients reporting significant depressive symptomatology increased. This was also tied to a decrease in social support and lower Karnofsky performance scores. These results suggest that functional status and the absence of social support likely contribute to the development of depression.

8.2. Treatment Type, Age, and Prior History of Depression

Some relationship has been observed between the type of treatment provided to the cancer survivor (e.g., chemotherapy, surgery, stem cell transplant) and depression. In a study of 63 women following chemotherapy for ovarian cancer, Hipkins and colleagues[44] assessed levels of anxiety and depression. Thirty-three percent of their sample met clinical criteria for depression immediately after discontinuation of chemotherapy. After 3 months, the rate of clinical depression dropped to 19% (though interestingly, the rates of anxiety disorders increased immediately from post chemotherapy). In their sample, medical parameters, such as stage of disease, response to treatment, Ca125 levels, and performance status were not associated with worse psychological outcome.

Middelboe *et al.*[45] assessed 36 patients before and after chemotherapy using the Hamilton Depression Scale (Ham-D), with scores greater than 12 qualifying as minor depression and greater than 17 as major depression. At baseline, prior to any chemotherapy, 12 (33%) individuals were between 13–17 and 5 (14%) were above 17 on the Ham-D. At 3-month follow-up, these percentages were 5 (17%) and 3 (10%) respectively, while at the 6-month follow-up 3 (13%) and 2 (9%) were above the cutoffs. As such, although nearly half the sample evidenced at least minor depression before treatment, by the end of treatment this had dropped to slightly over a quarter, with further reduction thereafter.

There appear to be few differences in rates of depression based on surgery type in breast cancer after 1 year postsurgery. Women receiving lumpectomy surgery as opposed to lumpectomy and radiation or mastectomy had higher rates of depression initially, but rates of depression were roughly equal between groups at 1-year follow-up.[46,47] Ganz and colleagues[48] report similar findings, with no differences in depression or emotional functioning in women receiving mastectomy versus lumpectomy at the end of primary treatment.

In a study of older adults greater than 5 years posttreatment, Deimling and colleagues[49] found a 25% incidence of depression. They hypothesized that increasing age may be a risk factor for depression. In addition, they found that individuals who had received chemotherapy were more likely to be depressed. Patients who continued to experience physical or functional impairment were also more likely to be depressed.

Hjermstad and colleagues[50] performed a prospective study of 128 patients undergoing conventional chemotherapy, autologous stem cell transplant, or allogeneic transplant and followed these patients for 3–5 years posttreatment. The authors found that patients receiving allogeneic transplantation displayed more symptoms in the first months posttransplant. In both transplanted groups, gradual improvement in functional status and symptoms occurred for 4–6 months, then stabilized at baseline levels. Only minor changes occurred after the first year. All groups reported more fatigue than population values after 3 years. Interestingly, the autologous transplant group reported less optimal quality of life and more fatigue compared to the allogeneic group, but there were no differences between groups in terms of depression.

Somewhat different findings were reported by Syrjala and colleagues[51] in a prospective, longitudinal study of 94 stem cell transplant survivors. The authors reported that only 19% of patients recovered fully by 1 year posttransplant, with the proportion of fully functional survivors increasing to 63% by 5 years. Patients who had more experience with cancer treatment before their transplant showed more rapid recovery from depression. Risk factors for depression after transplant included chronic graft versus host disease (GVHD), less social support before transplant, and female gender. Overall, there have been mixed results in terms of the impact of various treatments (chemotherapy, radiotherapy, surgery) on rates of depression. By and large, the type of treatment does not seem to have a significantly predictive role in depression. It does, however, appear that rates of depression are higher in individuals receiving the most intensive treatment (e.g., stem cell transplantation) and this appears related to the long duration to recovery.

Age has also been studied in terms of depressive risk. Deimling *et al.*'s[49] speculation that age may increase depression risk was contradicted by Schroevers, Ranchor, and Sanderman.[52] These authors conducted a longitudinal study, following three different age groups of cancer survivors over time from diagnosis to 8 years afterwards. They found that younger survivors were more likely to be depressed at the time of diagnosis and during treatment, but at 8-year follow-up, the group differences in depression were gone, suggesting no difference between groups in depressive risk years after treatment. These findings were similar to those of Weitzner *et al.*[53] who found no significant relationship between age and depression in long-term survivors. Overall, the available information suggests that age is not reliably correlated with depression.

As noted by Syrjala *et al.* above, depression after cancer treatment is also correlated with a previous history of depression.[54] Presence of depression and anxiety at time of admission has also been correlated with increased risk of depression after stem cell transplant.[55] In addition, availability of social support appears to lead to decreased risk of depression in patients with head and neck cancer.[56] In this same population, younger age, advanced disease, and lower performance status have been correlated with increased risk of depression after treatment ends.[57,58]

8.3. Coping Style and Depression

Cancer represents both an acute and long-term stressor, which can generate a variety of coping responses. Research has for some time investigated the ways in which coping during cancer treatment may impact psychological distress. Only recently, however, has coping been investigated in samples of patients who have completed cancer treatment. The implication of coping mechanisms on development of depression after cancer treatment is reviewed in this section. A brief caveat is in order: coping is a multidimensional concept, and has been measured using a variety of assessment techniques and theoretical models. Discussion of these theoretical constructs is beyond the scope of this paper, but readers are directed to the work of Deimling and colleagues[49] for a review.

Hack and Degner[59] performed a longitudinal study of the relationship between coping style and distress. They found that there was a positive correlation between acceptance/resignation at baseline (6 months or less after diagnosis) and depression at the 3-year follow-up. McCaul and colleagues[60] investigated recently diagnosed, early stage breast cancer patients and found that avoidant coping was associated with depression at baseline (time of diagnosis) and also at 4 months post-baseline. Moorey and colleagues investigated a relatively new coping questionnaire, the Cancer Coping Questionnaire (CCQ),[61] and found that greater use of coping strategies was associated with lower levels of depression. Nordin and Glimelius[62] assessed patients with gastrointestinal cancer during the period from diagnosis until 1 year later. They found that patients demonstrating helplessness/hopelessness at baseline were more likely to be depressed 1 year later. Schou *et al.*[63] found that cancer survivors displaying high levels of dispositional optimism were less likely to be depressed 1 year following initial surgery. The relationship between depression, coping strategies, and the approaches individuals take to a cancer diagnosis and treatment needs to be looked at in different cancers with different trajectories of recurrence or different mortality and morbidity profiles.

Schou's finding was replicated by Deimling *et al.*,[64] who investigated 321 older adults greater than 5 years post-diagnosis, and found that survivors with high levels of optimism were less likely to be depressed. In addition, survivors who utilized venting or denial as coping mechanisms were more depressed. The most powerful predictor of depression was functional impairment. Interestingly, the authors found that African-American survivors had significantly lower levels of depression than Caucasian survivors. The flip side of the trait of optimism is a tendency toward negativity (neuroticism), which was found to increase risk for depressive symptoms in one study of women after breast cancer surgery.[65]

In summary, it appears that the coping mechanisms utilized, and also the dispositional traits (i.e., optimism versus negativity) of cancer survivors may play a key role in predicting depression after cancer treatment ends. This relatively new area of research certainly merits further investigation and clarification in the future.

9.0. CONSEQUENCES OF DEPRESSION

Watson and colleagues[66] found that depression was correlated with significantly increased mortality at 5-year follow-up in a sample of breast cancer survivors. The authors note that the results should be interpreted with caution, given their small sample size. However, the results are nonetheless intriguing, and highlight the potential importance of assessing and treating depression in this population. Similar correlations between depression and risk of mortality have been found in lung cancer patients in one study,[67] and in stem cell transplant patients in another.[68]

Pretransplant depression has also been found to be associated with slower physical recovery after stem cell transplant.[51] In addition, women 2–4 years after breast cancer surgery (without recurrent disease) who report depression on the HADS have been found to request more medical testing and follow-up medical care[69] than nondepressed women. Another study investigated women treated with adjuvant radiation therapy and followed for an average of 2.5 years posttreatment.[70] The authors found that pretreatment depression was associated with chronic fatigue at follow-up.

10.0. BIOLOGIC THEORIES OF DEPRESSION IN PATIENTS AFTER CANCER TREATMENT

In general, psychological theories of depression related to cancer are better understood than biologic theories. The psychological correlates of depression related to cancer are well established. Cancer threatens not only one's life, but also changes one's self-image, vitality, activities of daily life, financial standing, interpersonal relationships, and role functioning. As such, there is a direct link between the interpersonal changes engendered by cancer and depressive symptoms.

As survival statistics continue to improve over time, research on biologic theories of depression after cancer treatment can be expected to increase. However, to date, no one has hypothesized a single, unifying theory of the biological causes of depression after cancer treatment. Many theories have been proposed regarding the pathophysiology of depression including deficits in neural transmission, viral infections, genetic mutations, and others.[71] Examining these theories in depth is beyond the scope of this review, though we will touch briefly on this area. For more in depth analysis, we refer the reader to a review of stress, medical illness, and depression.[72]

In general, biologic theories of depression have focused on the role of the neurotransmitters norepinephrine and serotonin. Most antidepressants work by increasing the availability of these transmitters to the brain, often by inhibiting reuptake by receptors. Several groups have studied the relationship between psychosocial factors, endocrine function, immune function, and survival (see Massie,[38] for a more thorough review), but none of these investigations to our knowledge have followed survivors after cancer treatment has ended. Therefore, there is a clear need for research investigating the role of cancer treatments (antineoplastics, radiotherapy, etc.) and other agents (psychotropics, benzodiazepines, hypnotics, Interferon, etc.) in the development and maintenance of depression after treatment.

Fatigue is often cited as a biological correlate of depression, though its relationship to depression is unclear, as fatigue and changes in sleep patterns can be a symptom of depression, or a symptom cluster independent of depression. Roscoe and colleagues[73] hypothesized that both depression and fatigue may be mediated by serotonin levels. They performed a double blind study of 94 female breast cancer patients randomly assigned to receive either 20 mg of paroxetine or a placebo. Assessment was performed via questionnaires. Interestingly, although depression was significantly reduced in the active medication group, no significant differences between groups were found in terms of fatigue. The authors suggest, therefore, that modulation of serotonin may not be a primary mechanism of fatigue.

Geinitz *et al.*[70] found a significant correlation between pretreatment depression and reported chronic fatigue at 2.5-year posttreatment follow-up in a sample of breast cancer patients treated with radiation therapy. Dimeo and colleagues[74] found no correlation between fatigue and thyroid, liver and kidney function, anemia, albumin concentration, or markers of immune activity in patients surviving treatment for hematologic malignancies. This leads to further questions about the relationships between depression and fatigue, as the biological mechanisms underlying both depression and fatigue are complex and appear to be interrelated in some studies but independent in others.

11.0. DIRECTIONS FOR THE FUTURE

There are many challenges for the future in terms of depression and cancer survivorship. In essence, the field is in its infancy, as grim cancer survival statistics have begun to turn around only in the past 30 years. Future research should focus on three broad areas: (1) better assessment of depression, its evaluation over time, and its relationship to other symptoms in cancer survivors, (2) research investigating coping style, risk of depression, and fluctuations in depression, and (3) development of effective interventions at various phases in cancer survivorship.

The challenge of better assessment can be addressed in several ways. First, research aiming to impact nurse and physician identification and treatment of depression would be very helpful. In one study of 456 outpatients, only 14% of patients identified as depressed were treated for depression.[75] Second, research clarifying the interaction between fatigue, pain, and depression would be helpful. At present, there is no universally agreed upon system for distinguishing between fatigue and depression, though work has begun in this area.[76] Finally, increased attention should be focused on the prevalence and pattern of nonclinical levels of dysphoria among cancer survivors, as well as its impact on daily functioning.

In terms of interventions, there are several areas with potential. First, given the relative scarcity of psychologists and psychiatrists in community oncology settings, interventions utilizing oncology nurses to identify and treat depression have shown promise.[77] Second, caregiver depression has recently become a focus,[78] and a number of emerging programs have proposed to treat caregiver depression in the hopes of improving quality of life for the entire cancer-affected family. Third, prospective trials continue to explore the role of support groups in mediating depression, and the functional components of these groups (see Goodwin,[79] for a review). Finally, the role of exercise in remediating depression has shown notable promise,[80] although some studies have found no beneficial psychological impact of exercise.[81]Coping style continues to be an active area of research interest in cancer survivors. It is clear that coping style and dispositional traits may play a large role in risk of depression after cancer treatment, and this will continue to be clarified and investigated. In addition, the relatively new concept of posttraumatic growth (also known as benefit finding) is an active area of research interest, and is essentially the "flip side" of the depression that is seen in some cancer survivors.[82] Why some individuals and caregivers are able to take the trauma of cancer and utilize this to find interpersonal benefit is under continued study, and may eventually shed light on the concept of depression and coping in individuals undergoing cancer treatment and possibly lead to better interventions in this area.

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Chapter 11

Interpersonal Relationships

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1.0. INTRODUCTION

Initial approaches to the problem of understanding the psychosocial impact of cancer focused largely on measuring changes in individual psychological functioning and quality of life in the short-term as patients coped with their diagnosis, change in health status, and invasive medical treatments. A large literature now attests to the fact that cancer is a stressful experience that may affect multiple aspects of psychological adjustment, including emotional well-being, social well-being, body image, sexuality, and physical functioning.[1–3] The majority of available research also suggests, however, that disruptions in quality of life and psychological functioning sustained by cancer patients are generally transitory and that most disease-free survivors demonstrate normative levels of psychological adjustment by a year or two following treatment.[2,4–7] Thus, most cancer-related distress appears to be short- rather than long-term in nature and can be expected to abate over time.

Conceptualizations of adjustment to cancer have evolved to include the interpersonal impact of the disease, in addition to its intrapersonal effects. For instance, it is now widely recognized that cancer may affect the psychological functioning of individuals close to the cancer patient, with some data indicating that partners of cancer patients may be at least as distressed as patients themselves.[6,8–11] In addition, as the field has developed, investigators have become increasingly interested in understanding the long-term implications of cancer for multiple aspects of survivor adjustment and well-being beyond the initial period of diagnosis and treatment.

The current chapter addresses relationships and interpersonal processes in cancer survivors. A broad view of cancer survivorship considers survivorship as beginning from the time of diagnosis, spanning the entire disease trajectory, and proceeding throughout the life span.[12] In keeping with the goal of this volume, wherever possible we attempt to focus our discussion on cancer survivors who have completed treatment and are considered disease-free, versus those who are actively undergoing or have recently completed treatment. However, as will be shown, at present relatively little research addresses relationship processes beyond the immediate diagnostic and treatment interval. In addition, we will focus on data acquired from adult cancer survivors and on the nonsexual aspects of interpersonal relationships. We also should note that extant data are limited in that the majority of studies addressing the impact of cancer on relationships have as their focus the partner or marital relationship. With regards to terminology, we use the term marital or spouse when the sample is comprised exclusively of married people, but use the more general term partner to refer to samples that may include unmarried individuals who identify themselves as partnered and when formulating general conclusions about the data. Also, in keeping with the broader literature on marital and partnered relationships, we use the terms relationship quality, satisfaction, and adjustment interchangeably.[13]

In considering the impact of cancer on interpersonal relationships we address the following questions: (1) What is the impact of cancer on the quality of interpersonal relationships? (2) How does cancer affect interpersonal processes such as communication, and what is the relationship between communication patterns and adjustment to cancer? and (3) What are the predictors of relationship quality in cancer survivors? We also address methodological limitations associated with existing data, suggest directions for future research, and discuss implications for those working clinically with this population.

2.0. THE IMPACT OF CANCER ON RELATIONSHIPS

Understanding the impact of cancer on relationships is important because cancer occurs in an interpersonal context. The diagnosis and treatment of cancer affect not only the patient, but also their significant others, including family and friends. Partners of cancer patients may experience significant decrements in physical, emotional, and social functioning that appear to parallel the patient's own response to their cancer.[6,14] Levels of adjustment in cancer patients and their partners also tend to be moderately positively correlated, suggesting that couples may have a mutual influence on one another[6,8,15] [for an exception, see ref. 16, where an inverse relationship between patient and partner adjustment was observed]. In addition to affecting individual components of quality of life and adjustment in each member of the dyad, cancer may affect role patterns and responsibilities, social activities, and the general emotional equilibrium of the couple.[14,17,18] These changes have potential ramifications for relationship adjustment and the ways in which members of the dyad relate to and support one another throughout the illness trajectory.[14,19]

Relationships and interpersonal processes are also important to examine because the cancer survivor's social environment plays a crucial role in their psychological adjustment to cancer. Relationships provide opportunities for individuals to receive both emotional and instrumental support, which are associated with better adjustment to cancer.[20–23] Although individuals with cancer may receive support from multiple categories of significant others, family members, particularly life partners, are their primary source of empathic support.[20,24] In fact, the presence of a positive partner relationship seems to be a key component of successful adaptation to virtually all aspects of the cancer experience.[20,24–26] Finally, interpersonal relationships form the basis for social functioning, which is widely regarded to be a critical minimum component of health-related quality of life assessments.[27–29]

Studies addressing the influence of cancer on relationships can crudely be categorized as falling into one of four methodological categories: (1) cross-sectional studies that compare relationship quality in cancer survivors and non-cancer controls,

(2) longitudinal studies that examine changes in relationship quality over time in cancer survivors, (3) studies documenting the overall level of relationship quality in cancer survivors, and (4) studies that retrospectively assess the perceived impact of cancer on relationship quality.

2.1. Relationship Quality in Cancer Survivors Compared to Healthy Controls

Several studies have compared relationship quality in cancer survivors to various control groups, both population-based and other. With few exceptions, the outcome of focus has been the partner relationship. In one of the earliest studies of this type, no differences in satisfaction with relationships with family or friends, or marital status were found between a mixed sample of 339 long-term (more than 3 years posttreatment), disease-free cancer survivors compared to national age-adjusted data.[30] In a more recent study specific to long-term testicular cancer survivors, no differences were found in separation or divorce rates compared to matched controls, and cancer survivors reported fewer negative changes in friendships compared to controls.[31] In an older study, also conducted with testicular cancer survivors, levels of satisfaction with the partner relationship were higher in survivors compared to age-matched controls.[32] Breast cancer survivors (between 6 and 57 months posttreatment) also have been found to report greater increases in their love for their partner compared to women with benign breast disease (BBD).[33] Data obtained from a sample of 5-year disease-free breast cancer survivors uncovered no differences between survivors and age-matched healthy women, or between women who sustained a recurrence and disease-free survivors, in the quality of the marital relationship.[34]

One of the prevailing myths about the impact of breast cancer on the marital relationship is that husbands desert their wives following treatment.[35] In a study designed explicitly to test this notion, secondary analyses were conducted comparing rates of marital breakdown and satisfaction in breast cancer cohorts and population-based controls.[36] For both survivors and controls, divorce and separation occurred infrequently (range: 1.6–11.5% of participants across cohorts of survivors and controls) and rates of marital dissatisfaction were low (range: 7.1–14.3% of participants across cohorts of survivors and controls). Marital breakdown was not higher in survivors compared to the controls. With regards to the satisfaction data, a similar percentage of women endorsed marital dissatisfaction across all cohorts of survivors and controls, with one exception: breast cancer survivors assessed 18 months following treatment reported higher levels of marital dissatisfaction (14.3%) compared to controls (7.8%). It should be noted that approximately 90% of the population in the study area were French-speaking and Catholic, which may have implications for the acceptability of divorce in this sample and constrain the generalizability of study findings.

One of the few studies to identify poorer dyadic adjustment in cancer survivors compared to controls comes from a sample of hematopoetic stem cell transplant (HSCT) survivors measured at least 12 months posttransplant (median = 6.6 years).[37] This is a unique population characterized by a high level of need for ongoing care that may extend for many years beyond treatment, and ultimately tax the dyadic relationship. Other studies with this population suggest that cancer patients report more positive changes in their partnered relationship than controls, but not in other relationship categories.[38]

2.2. Longitudinal Assessments of Relationship Quality After Cancer

Longitudinal investigations provide mixed findings regarding the influence of cancer on relationship quality. Declines in marital and family functioning from 60 days to 1 year postdiagnosis that were not observed in couples facing benign breast disease have been documented in women treated for breast cancer and their husbands.[15] We observed significant, but small, decrements in relationship quality over the first year following prostate cancer surgery for survivors, but not their partners.[6] Research conducted with long-term breast cancer survivors (at least 5 years postdiagnosis) also suggests that there may be small, but statistically significant decreases in the quality of the partner relationship over time; however marital status did not change from baseline to follow-up (time between assessments varied).[5]

However, other longitudinal data suggest that dyadic adjustment remains fairly constant over the first year following the diagnosis of breast cancer[39] and colon cancer[11] for both patients and their spouses, although family functioning in colon cancer patients appears to decline.[11] Data obtained from HSCT survivors and their caregivers suggest that relationship satisfaction is stable for survivors over the first year posttreatment; however, their partners may be at risk for worsened relationship quality at 6 months and 1 year posttransplant.[40] Analysis of change scores revealed that changes in relationship satisfaction were in the positive direction for 48% of HSCT survivors, but only 37% of their partners, who were also their primary caregivers. As suggested previously, the posttransplant course is known to place a high level of demand upon the caregiver for a sustained period following transplant that may uniquely place the partners of these survivors at risk for relationship strain.

2.3. Overall Levels of Relationship Quality

Descriptive data regarding overall levels of relationship quality in cancer survivors consistently indicate that functioning in this domain is excellent. The majority of women with breast cancer measured a year or more after diagnosis describe high levels of relationship satisfaction[16,39,41,42] as do patients actively in treatment.[43] Moderate-to-high levels of relationship quality have also been reported in women with recurrent breast cancer.[44] Even in those studies that reveal small decrements in relationship quality over time, overall marital adjustment tends to be high.[15] In our own research with prostate cancer survivors and their partners, we noted that overall relationship quality was excellent across the first year posttreatment for patients and partners,[6] echoing findings of other investigators working with this population.[45] Marital satisfaction also was high, and rates of marital distress were relatively low, in a sample of HSCT survivors measured a year posttreatment (14% of female patients and 7% of male spouse caregivers were distressed).[40]

2.4. Retrospective Evaluations of the Impact of Cancer on Interpersonal Relationships

Cancer survivors who are asked to reflect on the impact of cancer on their significant relationships report that the changes associated with the cancer experience are largely positive rather than negative.[46] In fact, positive changes in relationships with others is one of the most frequently cited domains of benefit-finding by cancer survivors across virtually all cancer diagnoses, with between 50 and 85% of cancer survivors endorsing this change.[46–48]

In an early study of breast cancer survivors 2.5 years posttreatment and their husbands, 89% of survivors and 85% of husbands described the impact of cancer on their marriage in positive terms.[49] In addition, 81% of survivors and 65% of patients described the impact of breast cancer on relationships with children as positive; and 68% of survivors and 63% of husbands regarded the impact on relationships with friends as positive.[49] Although nearly half of women who had breast cancer in another study reported no changes in their relationships with their children, 73% of the women who endorsed some degree of relationship change regarded the changes as positive, citing increased closeness and understanding.[50] In a sample of breast cancer survivors and their husbands assessed 1 year following diagnosis, 42% of couples ($N = 282$) were in agreement that breast cancer had brought them closer, 16% regarded cancer as having no impact on relationship closeness, 34% were discordant (i.e., only one member of the couple reported a sense of increased closeness), and only 7% of couples were characterized by perceived distancing in one or both members.[51] Likewise, the overwhelming majority of long-term testicular cancer survivors (82%) and their wives (85%) reported that their experience with cancer drew them closer as a couple.[52] Although reports of growth in the relationship domain are ubiquitous, some data suggest that strengthening of intimate relationships may be more prevalent in married than nonmarried cancer survivors.[53,54]

Approximately half of patients undergoing evaluation for bone marrow transplantation reported that their cancer had led to improved relationships with their spouse or partner (57%), children (49%), or friends (43%), and 68% described experiencing more love for their spouse/partner after diagnosis.[38] In another study of bone marrow transplantation survivors who ranged from 6 to 149 months posttransplant, significantly more positive than negative changes in relationships with various categories of family members, including siblings, parents, children, and spouse were reported.[55] It also should be noted, however, that examination of frequency data for reports of no change were generally comparable to or higher than either the positive or negative category.

2.5. Summary

Data acquired via various methodologies suggest that the overwhelming majority of people diagnosed with cancer report high levels of relationship quality over the course of survivorship. Most studies have focused on the partner relationship, however the few studies conducted with other categories of family and friends are also indicative of high-quality relationships. In fact, survivors themselves tend to recall their interpersonal relationships as having been changed for the better, if at all, by the cancer experience.

A few longitudinal studies suggest that there may be small decrements in the quality of the partner relationship over time, particularly over the first year postdiagnosis, however reported declines are generally small and of questionable clinical significance. In addition, global relationship quality remains excellent, making it difficult to formulate strong conclusions about the meaning of these data. Although longitudinal data generally represent our best source of information about how functioning in a given area changes over time, the fact that we are precluded from measuring relationship quality prior to the cancer diagnosis further limits interpretations about the impact of cancer on relationship functioning. Observed decrements in relationship quality over time may reflect a trend observed in the broader marital literature,[13] and may not be attributable to the cancer experience.

Although global relationship quality is good for the majority of cancer survivors, it is possible that measures of overall relationship satisfaction fail to capture or obscure subtle areas of strain experienced by cancer survivors in the relationship domain. One component of relationship quality that has received some attention is the quality of communication between the survivor and their partner. We turn to this next.

3.0. COMMUNICATION PROCESSES AND SOCIAL CONSTRAINTS IN CANCER SURVIVORS

3.1. Communication and Interpersonal Processes in Cancer Survivors

Clinical experience and empirical data indicate that communication is an important contributor to good relationship adjustment.[56] Couples who are able to maintain open communication throughout the cancer experience report better marital adjustment than those who experience communication problems.[57] Patient and partner perceptions regarding how they communicate about cancer-related issues are associated with relationship satisfaction and psychological functioning.[24,58–60] Open discussions about the cancer experience may facilitate patients' and partners' abilities to meet their support needs and maintain or build intimacy.

Unfortunately, communication patterns and support processes may be disrupted as survivors and individuals in their support network navigate the cancer experience. Such difficulties may not be confined solely to low-quality relationships. Many women with breast cancer report isolated instances of rejection and withdrawal, most frequently from their significant other.[61] Other examples of unhelpful behaviors described by cancer survivors include criticism about their response to cancer, minimization of the impact of cancer, and overt expressions of worry or pessimism about the illness, which can contribute to feeling misunderstood and undermine open communication.[58,62] In fact, cancer survivors rate difficulties with communication as their biggest relationship problem area.[12,41] In one study, approximately a third of cancer survivors identified difficulties communicating with their partner as frequent and severe, a problem that was particularly pronounced for those diagnosed with lung cancer.[12] Cancer survivors also identify the need for additional opportunities to express and process ongoing threats associated with their cancer after treatment is completed, which may be unacknowledged by their family or friends.[61] Partners and other family members may wish to return things to the way they were prior to diagnosis and not wish to discuss matters regarding cancer any longer. Family members and partners also may have a tendency to avoid discussing sensitive issues related to the survivor's cancer, especially topics related to recurrence, or end of life, for fear that talking about these topics will be distressing to the survivor.[12,41,58,63]

Although unsupportive patterns of communication appear to occur relatively infrequently in samples of cancer survivors,[64–67] existing data suggest that when they do occur they may play a stronger role in predicting (worse) psychological adjustment than do supportive behaviors.[67,68] Thus, particular attention to these negative behaviors and the mechanisms whereby they exert their effects on psychological functioning is warranted. Understanding the interpersonal processes that may be problematic for cancer survivors is also a crucial step to identifying and targeting patients for psychological intervention.

3.2. Social Constraints

A growing literature examines the impact of social constraints, or unsupportive behaviors directed towards individuals by members of one's support network that cause the individual to feel misunderstood or alienated, on adjustment outcomes following cancer.[67,68] Researchers in this area have distinguished between two forms of socially constrained behavior: criticism, and avoidance or withdrawal.[69] Thus, socially constraining behaviors may be expressed passively or in more overtly critical and hostile manners. Social constraints are associated with poorer adjustment to cancer, and relationship distress.[64,70,71]

The social cognitive processing model of adjustment to cancer provides a context for understanding the impact of social constraints on cancer survivors.[64,72] According to this model, a supportive social network fosters adjustment to stressful events, such as cancer, by providing an atmosphere in which one's thoughts and feelings about their illness can be freely discussed and worked through. Such interactions may be beneficial because they are inherently validating, because they facilitate the maintenance of self-esteem, or because they provide the survivor with feedback about how she or he is managing the experience that enhances their perceptions of control or ability to cope.[72] Conversely, unsupportive interpersonal interactions are postulated to inhibit the free discussion and discourse that enable a patient to adequately process the cancer experience and reduce distress.[69,70,72]

Some support exists for this model. Social constraints are associated with higher levels of intrusive and avoidance symptoms, less talking about the cancer, and other markers of ongoing difficulty processing the cancer experience.[64,70] In addition, intrusive thoughts related to the cancer experience appear to be particularly distressing for individuals who function in a socially constrained environment, suggesting that constraints may interfere with cognitive processing.[64,69] Social constraints from one's partner appear to be more deleterious than constraints from other family or friends.[64] Data also indicate that the relationship between unsupportive or socially constrained behaviors and psychological functioning is at least partly mediated by indicators of ongoing cognitive processing such as cancer-related intrusions and avoidance symptoms.[22,64,70] However, the relationship between social constraints from one's partner and psychological distress in the survivor is not explained by reduced disclosure on the part of the cancer survivor.[69] In addition, there are data suggesting that the mechanisms linking social constraints to distress may differ depending on the nature of the relationship and source of the constraints. For instance, in one study avoidance of cancer-related thoughts mediated the relationship between constraints from friends and family and mental health; however the relationship between partner constraints and mental health was not mediated by avoidance, suggesting a more direct relationship between partner constraints and patient adjustment.[64] Other data suggest that impaired self-esteem mediates the relationship between unsupportive behaviors from friends and family members and patient psychological distress.[73]One of the most consistent findings to emerge is that social constraints from one's partner lead to distress by increasing maladaptive, avoidant-based coping strategies and contributing to negative appraisals of coping efficacy.[74,75] Thus, the partner relationship seems to provide a critical source of feedback for patients about their coping behaviors. Partner constraints may have a particularly damaging impact on the coping repertoire of cancer survivors who do not have adequate reserves of support from other family and friends. In one study examining this issue, the relationship between unsupportive spouse behaviors and both coping efficacy and avoidance was strong and significant only for women with lower levels of friend and family support.[65] For women with higher levels of support from family and friends, partner unsupportive behaviors were not associated with avoidance or coping efficacy. In addition, the relationship between unsupportive spouse behaviors and distress was mediated by reduced coping efficacy for those with low family/friend support only.[65]

3.3. Summary

To summarize, a growing literature indicates that unsupportive or constraining behaviors in the cancer survivor's social environment are risk factors for distress. Social constraints may impair adjustment to cancer by interfering with cognitive processing. Although social constraints are associated with markers of ongoing difficulty processing the cancer experience, social constraints do not seem to exert their effects on distress by reducing cancer-related disclosure. Social constraints from partners appear to adversely affect coping appraisals and coping behaviors, which, in turn, are associated with poorer adjustment to cancer. However, the cross-sectional nature of the bulk of the data limits the formation of strong inferences.

4.0. CORRELATES OF RELATIONSHIP FUNCTIONING AFTER CANCER

Given that the majority of cancer survivors describe high levels of relationship quality, the more interesting question from a psychological standpoint may not be how relationships change after cancer, but rather for whom they change and why. Such data are crucial to identifying individuals and relationships that may be at risk for maladjustment and developing intervention strategies to improve survivor outcomes in this domain. We now turn to addressing the medical, demographic, and psychological variables that may be associated with relationship outcomes following cancer. Virtually all of the available data address the couple or partner relationship, which will also be the focus of our review below unless otherwise noted.

4.1. Illness-Related Variables

Disease and treatment severity. Characteristics of the illness, including disease stage, treatment, and time since diagnosis predict psychological adjustment and quality of life in cancer patients.[2,5,12] Given this, one might anticipate that these variables would have implications for relationship functioning as well. However, few studies have investigated the impact of illness- or treatment-related variables on relationship functioning specifically. In a cross-sectional study, no differences were found in relationship satisfaction, the expression of affection, or cohesiveness in partners of patients at four stages of the illness trajectory, including initial diagnosis, first remission, first recurrence, and metastatic disease.[76] Other data suggest that women with recurrent breast cancer report equivalent levels of relationship satisfaction to disease-free survivors and matched controls without cancer.[34,44]

There are, however, a few exceptions to these findings. In one of the only studies that explored the role of illness severity on relationship problems between mothers with breast cancer and their children, relationship problems and poorer prognosis were significantly correlated.[50] However, this study did not tease apart the unique contributions of illness-severity (prognosis) and treatment-severity (surgery), which was also linked to relationship problems. Treatments that are more severe and physically debilitating may be associated with a higher degree of disruption to interpersonal relationships because they cause more role limitations.[77]

More invasive surgery (mastectomy versus lumpectomy) has been linked to poorer marital adjustment in breast cancer patients and their husbands[61] and more relationship problems between breast cancer patients and their children.[50] Results of a meta-analysis that examined the impact of breast conserving surgery versus mastectomy on marital and sexual functioning suggest that mastectomy may be associated with worse functioning, however the effect size was small.[78] Higher levels of marital dissatisfaction have also been observed in the spousal caregivers of patients who underwent more intensive HSCT regimens (allogeneic versus autologous transplants).[40]

Treatment regimens that are more physically debilitating, or are associated with prolonged caregiving (such as stem cell transplant) may be more disruptive to the couple's relationship as roles and responsibilities are altered for extended periods of time. Data indicate that patient functional impairment may restrict the spouse's ability to participate in their usual activities, which can lead to higher levels of negative mood in the spouse.[43] Impairments in patient physical functioning[79] and illness-related demands[80] also are associated with lower levels of marital satisfaction in cancer patients and their spouses.

The severity of the illness also may exert its impact on relationship functioning via patients' and family members' perceptions about the cancer, and the effects of these perceptions on patient and partner distress. For instance, the relationship between illness severity and poorer psychological adjustment in cancer patients appears to be mediated by cognitive variables such as hopelessness.[77] Perceptions about illness severity are related not only to patient distress, but also to distress in their spouse and children.[1,81,82] Other study results support these findings, concluding that it is not entirely physical symptoms related to the cancer or medical factors per se that contribute to psychosocial problems in patients and partners, but also appraisals about the illness can have a significant impact on adjustment.[83]

In summary, although illness-severity variables such as disease prognosis and recurrence do not appear to account for large portions of the variance in relationship functioning, more severe treatments may place patients and partners at risk for relationship distress. Possible mechanisms for the association between treatment severity and dyadic adjustment include increased disruption to patients' physical functioning, illness-related demands that tax the partner's resources, and perceptions about the severity of the illness and treatment, all of which may contribute to psychological, and ultimately, couple distress.

Time since diagnosis or treatment. A sizeable literature suggests that the period surrounding diagnosis and treatment is particularly challenging and stressful for cancer patients.[84,85] Presumably then, the impact of cancer on relationship functioning may also be most pronounced during this period of time, as patients and their loved ones adjust to and cope with changes in health status and role functioning. Time since completing treatment was moderately positively correlated with marital satisfaction in one small sample of breast cancer survivors.[86] In general, however, time since diagnosis or treatment has not been included as a predictor of relationship quality. Also, as discussed above, longitudinal data do not support the idea that relationship satisfaction improves over time.

Several investigators have examined patterns of communication and support in cancer survivors over time. Consistent with our clinical experience, the data suggest that some cancer survivors have an ongoing desire to communicate about their experience with cancer that persists long after treatment has been completed.[58,61] In one of the few studies to examine the evolution of cancer-related communication over time, patterns of communicating about cancer were stable over the first year or so following cancer treatment, suggesting that the transition to survivorship may require ongoing communication within the couple.[60] Alternatively, the stability of communication may simply have been a by-product of the fact that most participants were in highly satisfied, stable relationships that were likely characterized by stable and adaptive communication patterns.

Although survivors may have a need for ongoing support related to the cancer experience, research indicates that supportive behaviors from members of one's social network may decline as the patient moves further from treatment.[20,87] In addition, increases in patient emotional distress over time may lead to the erosion, rather than provision, of support.[87] Cancer survivors who are distressed and/or have ongoing needs to communicate and receive support about the cancer experience seem likely to be at risk for relationship disruption. Also, couples may have a tendency to avoid addressing relationship problems during the initial phases of the illness, such that relationship problems may accumulate over time, and only emerge once the acute stress associated with diagnosis and treatment subsides.[88] Finally, cancer treatments with ramifications for intimate aspects of the couple's relationship (such as radical prostatectomy) or those requiring ongoing caregiving (such as HSCT) may be associated with longer term reductions in marital satisfaction.[6,12,40]

To summarize, few investigators have examined time since treatment or diagnosis as a predictor of relationship functioning after cancer. However, existing data suggest that survivors who experience prolonged psychosocial impairments or have ongoing caregiving needs may be at risk for relationship distress.

4.2. Demographic Variables

Clinical experience suggests that some demographic characteristics may have implications for how couples maneuver through the cancer experience. In this section we focus on a few specific demographic variables that have been linked to relationship functioning in cancer survivors including gender, role status, age, and length of relationship.

Gender and role status. Although most researchers have focused their attention on the influence of gender on psychological adjustment in response to cancer, a few studies have examined the impact of gender on relationship functioning specifically. Existing data suggest that women report lower levels of marital satisfaction and more role problems than men, regardless of whether they are the patient or spouse.[11] Levels of marital satisfaction following HSCT also are lower in female compared to male partners.[40] These findings are consistent with the larger literature regarding the impact of chronic illness on marital functioning which suggests that women may be more likely than men to experience worsened marital satisfaction when their spouse suffers from chronic illness.[18]

The relation between female gender and poorer relationship quality may be partly attributable to the differential impact of cancer on the psychological adjustment of women versus men. Several studies suggest that women are more vulnerable to psychological distress than men following cancer.[8,11,76,89] In addition, women's distress appears to be independent of their role as patient or partner/caregiver.[8,11,76,90]

Data on the relationship between gender and distress are not entirely consistent, however. Higher levels of distress have been reported in male spouses of colon cancer patients compared to their (female) partners and male patients[9]; and male spouses of melanoma patients compared to female spouses.[89] Other research suggests that male patients are at higher risk for distress than male partners.[90]

Although very few studies have examined the relationship between gender and relationship quality as an outcome variable, available data are suggestive of lower levels of relationship satisfaction in women compared to men, which may be related to their higher levels of emotional distress. However, gender and role are frequently confounded, which further complicates the interpretation of study findings. Consideration of role (patient or partner) as well as gender may be important in the context of understanding relationship functioning and psychological adjustment to cancer.

Age and length of relationship. Data linking age to global relationship adjustment following cancer are inconclusive. Although the trend in the literature is to assume that younger patients are at risk for relationship problems, the data are not consistent. Some investigators have found no relationship between age and marital satisfaction[40] or problems with role adjustment[83]; while still others have reported an inverse relation between age and marital satisfaction.[61]

Several other studies have identified younger age as a risk factor for specific relationship problems, however. For instance, younger female cancer patients report poorer partner communication than older patients.[42] In a tri-ethnic sample of early-stage breast cancer patients, younger age was associated with more partner-related concerns (e.g., concern about arguing with partner or being rejected).[91] Perceptions of spouse criticism and spouse avoidance are also higher in younger than older cancer patients.[74] Younger cancer patients also tend to report poorer quality of life,[92] more psychosocial problems,[91] and greater impact of cancer on life plans and activities[5] which may partly explain their apparently higher levels of disruption in some components of relationship functioning.

The inconsistencies in the literature regarding the association between age and relationship adjustment highlight the importance of considering third variables that may explain the conflicting findings. On a related note, age and length of relationship are usually confounded, making it unclear to which variable any observable relationship should be attributed. Thus, future research should also examine the impact of cancer on the marriages of younger versus older couples.

4.3. Psychological Distress

Psychological distress has been linked to relationship quality in cancer survivors and their partners.[16,39,79,93] Not surprisingly, cancer patients who are in less satisfying relationships endorse higher levels of psychological distress.[43] Distress in one member of the dyad also may be related to the level of marital satisfaction reported by their partner.[16,79] Negative behaviors from one's partner, including social withdrawal and other kinds of unsupportive behaviors, have been found to predict patient psychological distress.[74,75] Available data suggest that patients' perceptions about relationship processes such as communication are more strongly linked to both patient and partner distress and relationship satisfaction than partners' perceptions.[16,60]

Although few data address distress as a predictor of relationship quality, a growing literature supports the idea that relationship quality may play a role in attenuating psychological distress in cancer survivors. The relationship between avoidant and intrusive stress symptoms and negative mood appears to be less pronounced for prostate cancer patients who endorse higher levels of relationship satisfaction.[94] Other data suggest that the mechanisms accounting for the relationship between patient functional impairment and partner distress or partner negative behaviors may differ in high versus low satisfaction marriages.[43]

Although psychological adjustment and relationship functioning are clearly correlated, the direction of the relationship remains unclear. Most available research emphasizes the role of relationship functioning in predicting psychological distress rather than vice versa, however the cross-sectional nature of the bulk of the data precludes establishing the direction of the relationship. Furthermore, it seems quite likely that the relationship between these variables is bidirectional. Data suggest that psychological distress and maladjustment may be more prevalent in relationships that are low in satisfaction, and that the presence of a good quality partner relationship may buffer against psychological distress.

4.4. Relationship Quality

The perceived quality of the couple's relationship prior to cancer appears to be a strong predictor of marital satisfaction following cancer.[66] Couples who recall having experienced higher levels of marital satisfaction prior to diagnosis tend to endorse higher levels of satisfaction following diagnosis and treatment.[61] The quality of the marital relationship in the early stages of the illness experience also appears to predict future problems. In one study, low marital satisfaction identified within the first 3 months of diagnosis predicted both marital dissatisfaction and marital dissolution at later time points.[36] Not only does relationship dissatisfaction predict later relationship quality, but also it is a significant predictor of concurrent and future psychological distress.[39] Thus, couples experiencing relationship problems prior to the cancer experience may be at increased risk for difficulties during and following the cancer experience.

4.5. Summary

Few studies have explored predictors of relationship quality following cancer. In large part this is due to the fact that relationship quality is more frequently conceptualized as a predictor of adjustment rather than an outcome variable. Although the data are not entirely consistent, patients who are younger, female, who undergo more severe or invasive treatments, or experience prolonged caregiving requirements or psychological distress, may experience higher rates of relationship dysfunction. Relationships that are designated as unsatisfactory early on in the cancer trajectory are clearly at risk for future dysfunction.

5.0. METHODOLOGICAL LIMITATIONS

Although the data that we have reviewed thus far indicate that functioning in the interpersonal domain is good for the overwhelming majority of cancer survivors, it is important to note several limitations in the existing literature. First, most studies have used retrospective methodologies. Because of this, we know more about the perceived impact of cancer on relationships than actual changes that may occur in relationships over time.[18] Several factors may lead the cancer survivor to overestimate or underestimate the positive or negative influence of cancer on their interpersonal relationships. Relationships with members of one's social environment may seem poorer following cancer because of the multiple stressors associated with managing the cancer diagnosis and associated burden.[18] Alternatively, survivors or their significant others may be motivated to suppress negative feelings about their relationship to reduce feelings of guilt, which may lead to an overestimation of their post-cancer relationship quality. Couples dealing with cancer also may feel obligated to maintain their relationship even in the face of existing difficulties, a tendency that may be especially pronounced early on in the treatment and recovery course when patients are in need of additional support and assistance. Finally, social–cognitive processes such as cognitive dissonance may cause the survivor or partner to evaluate the relationship as being more positive than it actually is.[18]

Longitudinal research that tracks actual changes in relationship functioning over time is also not without its problems, however. First, although there are exceptions, most longitudinal studies address changes in relationship quality over the first year or two following diagnosis and treatment, and speak less to the potential impact of cancer on relationships in long-term disease-free survivors. In addition, even when longitudinal data are available, study participants are only identified postdiagnosis after they have learned that they have cancer. Although this issue may be less relevant to the focus of the current volume on survivorship, a pre-cancer assessment of relationship functioning would be required to truly address the impact of cancer in this domain, which clearly represents a major challenge to the field.[14] Finally, the possibility that observed deterioration or improvements would have occurred in absence of cancer remains.

In addition, most of the literature addressing communication and relationship processes has been conducted with patients who are actively involved in treatment. It is not clear if the same processes apply to long-term survivors, or how relationship processes and interaction patterns evolve over time as the individual transitions into long-term survivorship.

Another major limiting factor in this area relates to sample bias and generalizability. Although this problem is by no means unique to studies addressing relationship functioning after cancer, issues related to selection bias may be amplified in studies examining relationship functioning and interpersonal processes, particularly when research designs require participation of both members of a couple and/or participation across multiple time points.[14] Data show that participation rates for couple-based psycho-oncology research tend to be lower than individual-based research [e.g., 51% participation rate in ref. 6; 54% in ref. 69; 56% in ref. 65]. Couples who agree to participate in intensive research programs such as these are likely in highly supportive relationships and may not be representative of the broader population of cancer survivors and their partners. This notion is borne out in the generally high overall ratings of relationship quality observed in most studies [for examples see refs. 6, 60, 65]. In fact, relationship satisfaction in study participants that may be classified as "low" for comparison purposes tends to be good compared to conventional norms.[43] In addition, attrition rates are higher in individuals endorsing lower levels of relationship satisfaction, less adaptive communication patterns, and fewer years of partnership/marriage.[6,60] Thus, we may be failing to capture those survivors and couples who are experiencing relationship distress. Finally, because cancer is generally a disease of aging, most participants in couple-based investigations are older couples who have been married or partnered for many years.[6,43,45]

Couples in lengthy partnerships have likely endured other hardships and challenges throughout the course of their duration as a couple, which may make them better equipped to manage the stressors associated with cancer as well, and they may be more committed to the relationship given their investment in it. Not only does the fact that most research is conducted with individuals and couples in long-term relationships reporting high levels of relationships satisfaction and few problematic relationship behaviors threaten the generalizability and external validity of findings, but also this issue is problematic because it leads to restriction of variance, which ultimately reduces statistical power and ability to detect significant effects.

Finally, the literature on relationships and relationship processes also is not immune to the general limitations to generalizability found in most psycho-oncology research. Most studies are conducted with samples comprised of highly educated, Caucasian women diagnosed and treated for breast cancer and their male partners, and it is unclear how well these findings apply to other cancer survivors and their loved ones.

6.0. DIRECTIONS FOR FUTURE RESEARCH

Most of what we know about the interpersonal processes involved in adjustment to cancer is restricted to the dyadic relationship. More systematic research assessing the impact of cancer on relationships with other family members and friends is needed to clarify how interpersonal processes are affected by the cancer experience. For instance, although there is a growing literature that addresses the impact of cancer on psychological outcomes in children of cancer patients,[95,96] very few studies have addressed the impact of cancer on relationships with one's children. In addition, much of the research investigating relationship processes such as communication and social constraints is based on samples of survivors who are still undergoing or only recently completed treatment. Data regarding the long-term impact of cancer on relationship processes and their association with psychological and quality of life outcomes are needed.

The majority of studies are based on self-report indicators of relationship satisfaction or communication, and very few studies have directly observed patterns of interaction between couples [for an exception see ref. 71]. However, relationship functioning is an interactive process, and studies that focus on the perspective of only one member of the couple may fail to capture dynamic processes as they unfold in the dyad. Data suggest that patients and their spousal caregivers may differ in their perceptions of the impact of the illness on various domains of functioning, including the marital relationship,[97] and communication patterns,[58,60] pointing to the importance of considering the viewpoints of both members of the relationship dyad. Self-report data also may be influenced by stable dispositional variables.[67] Observational data may shed unique insights onto relationship functioning that are not captured when study participants are asked to reflect and report on their level of adaptation and functioning in this domain.

There also is clearly a need for research with more ethnically and culturally diverse populations. The few culture-specific studies that are available suggest that there are few differences between ethnic and nonethnic samples on standardized measures of marital functioning, however qualitative data suggest that the cultural norms related to expression and gender role expectations may contribute to relationship quality.[98] Data that evaluate the impact of cancer on nonmarital relationships

Table 1. Key Areas for Future Research

Future research should address:
1. Nonmarital, partnered relationships
2. Relationships with other family members and friends
3. Observational data of relationship interactions
4. Culturally and ethnically diverse samples
5. Theoretical models of relationship adjustment
6. Components of relationship functioning versus global relationship quality
7. Predictors of poor relationship outcomes
8. Predictors of positive relationship outcomes
9. Relationship outcomes and processes in long-term survivors

also are needed, including those comprised of same-sex partners, particularly in light of data suggesting that gender may moderate the influence of cancer on psychosocial and relationship adjustment and data suggesting that unmarried partnerships may be at greater risk for strain than strengthening compared to married partnerships.[53]

In addition, studies examining the impact of cancer on relationship functioning are largely descriptive. Research that provides a theoretical context for understanding the potential impact of cancer on relationships and interpersonal processes is required. That is, what are the theoretical reasons for expecting relationships to deteriorate, worsen, or maintain equilibrium at different points in the survivorship trajectory? For instance, prominent theories of adjustment to traumatic or stressful events increasingly incorporate the potential for positive changes in interpersonal relationships following stressors such as cancer, and provide a context for considering how positive changes might occur and potential predictors of positive outcomes.[99–101] In addition, general theories about marital and relationship functioning such as social-exchange theory, crisis theory, and equity theory may prove useful in generating future theoretically derived hypotheses about the impact of cancer on relationship functioning and interpersonal processes.[13]

Given that global relationship functioning is good for the majority of cancer survivors in existing research, we need to turn our attention to identifying components of relationship functioning that are at risk for strain across the disease and survivorship trajectories. It also will be important to determine whether maladaptive patterns of interaction are emblematic of long-term dysfunctional relationship patterns or reflect stress-related changes specific to the cancer experience that resolve over time. Future research should be targeted toward identifying survivors and members of their social network who are at risk for poorer psychosocial and relationship outcomes.

Finally, although it is important to identify markers of risk for relationship and other psychosocial problems, we should also add that the literature may benefit from elucidation of variables that predict positive adjustment in these domains. These data may improve our understanding of adaptive relationship processes, and also assist in developing psychological interventions. Unfortunately, scant research has addressed predictors of benefit-finding specific to the relationship domain and this may be an important direction for future investigation (see Table 1).

7.0. CLINICAL IMPLICATIONS

Although the overwhelming majority of cancer survivors endorse good relationship adaptation, a subgroup of patients, their partners, or family members may experience impairments in relationship quality or interaction patterns deserving of clinical attention. One of the major lessons that we take after reviewing the literature in this area is the importance of asking about specific components of relationship functioning versus focusing solely on perceptions or ratings of global relationship quality. Thus, we suggest that clinicians working with cancer survivors or members of their social network inquire specifically about communication and support patterns between the survivor and their significant others [see also ref. 60]. In addition, couple-focused interventions may be indicated when cancer-related communication problems are identified,[43,94] particularly given the relationships between partner responses and patient coping and distress outcomes, and the protective effect of dyadic adjustment on psychological distress.[94]

Clinically, reducing negative interpersonal interactions may have a more profound impact on psychological adjustment than increasing supportive interactions.[67,68] However, interventions that improve the couple's ability to appropriately give and receive support after cancer also appear to improve relationship quality and distress.[14,102] Survivors themselves may benefit from learning how to express their worries and concerns in a manner that increases rather than decreases supportive partner responses.

Finally, intervention efforts also should be targeted toward those at increased risk for distress. Although our conclusions can only be described as tentative, we suggest that female survivors and family members who are dealing with more invasive treatment regimens, are younger or in newer relationships, have fewer support resources, and are in relationships that are troubled prior to the cancer diagnosis may be at the highest risk for maladjustment. Given that relationship distress measured early on in diagnosis and treatment is a particularly potent predictor of later relationship dysfunction, efforts should be focused on early identification and treatment of relationship problems.

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Chapter 12

Adaptation in the Face of Advanced Cancer

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1.0. INTRODUCTION

Scientific understanding of cancer as a physical and psychological challenge to those affected by it has progressed markedly in the last few decades. Medical advances have improved the prognosis for many cancers, allowing individuals to live longer with active advanced-stage disease. Individuals living with advanced cancer (AC) are receiving increased empirical attention, as this growing population faces adaptive challenges that are quite different from those of survivors of early-stage disease.

In this chapter, we review the existing literature on psychosocial adaptation to AC. Our goals are to (1) describe the population of individuals with advanced disease; (2) discuss the experience of those living with AC, highlighting the unique adaptive tasks that this group may face; (3) examine potential predictors of psychological adjustment, including medical variables, contextual factors, and individual differences in personality and coping; (4) describe psychosocial interventions that may facilitate adaptive outcomes in this population; and (5) address potential directions for future research and clinical practice. Although much of the existing research in AC deals with end-of-life concerns, the scope of this chapter precludes a review of that literature, as we will focus on individuals living with advanced disease prior to that phase.

2.0. WHO ARE THE INDIVIDUALS WITH ADVANCED DISEASE?

The National Cancer Institute defines a cancer survivor as any individual who has received a cancer diagnosis "who is still living . . . no matter when that diagnosis was made or whether it was successfully treated."[1] Thus, people with AC that has metastasized to tissues distant from the original tumor site are classified as "survivors" from the moment of diagnosis until death, regardless of prognosis or disease activity.

To many laypeople, practitioners, and patients themselves, this group may not fit their prototype of a posttreatment, disease-free survivor. Indeed, some people with AC choose not to call themselves survivors when treatment has not eradicated the disease and they face a foreshortened future, believing that the term portrays a more optimistic state of affairs than is warranted.[1] Nevertheless, individuals with AC have been underrepresented in cancer survivorship research and activism, and we believe that the unique issues they face deserve a place in this handbook.

Although some issues and concerns may be common across individuals with AC, it is an extremely heterogeneous population. Nearly all cancers have the potential to metastasize through the bloodstream, the lymphatic system, or by local extension of the primary tumor to the surrounding tissues. Common sites of metastases include the brain, lungs, liver, abdomen, skin, and bones, and the location of metastases often depends on where the cancer originated.[2] Cancers that have metastasized are usually incurable. Nevertheless, treatments can frequently shrink or control the tumor, relieve physical symptoms, and prolong life. Treatment of AC may include radiation to target metastatic lesions in the brain or the bones, chemotherapy, or, depending on the location and size of the lesions, surgical resection of metastases to the brain, lungs, or liver. As cancer treatments can be accompanied by adverse side effects such as fatigue and nausea, the potential advantages of various treatment options for AC must be weighed against potential risks and effects on quality of life (QOL).

For some cancers where early detection is difficult or tumors particularly aggressive, such as ovarian or pancreatic cancer, a patient may not be diagnosed with cancer until it has metastasized and is no longer curable. For others, AC arises as a recurrence of earlier malignancy after a period of remission. An individual's experience of being diagnosed with advanced disease may be quite different depending on whether it is a first cancer diagnosis or a recurrence.[3] For example, receiving a previous diagnosis of early-stage disease may grant individuals additional time to consider the possibility of a foreshortened future should their cancer metastasize, whereas an initial diagnosis of Stage IV cancer can overwhelm patients with immediate end-of-life concerns. Prognosis of AC is also quite variable, depending on the disease site, the treatments available, the extent of metastasis, and many unknowns. Although most people diagnosed with AC survive less than one year,[2] others live for decades with metastatic disease. The cancers most likely to be diagnosed at an advanced stage include lung cancer, gastrointestinal cancers (i.e., colon and rectum), non-Hodgkin lymphoma, and ovarian cancer.[4] Given the high prevalence of breast and prostate cancers, many individuals with metastatic disease also fall into these diagnostic categories, although they are more likely to have a previous diagnosis of early-stage disease.

3.0. ADAPTIVE TASKS IN LIVING WITH ADVANCED CANCER

To date the psychologically relevant issues receiving the greatest attention in this population have been pain, fatigue, and depression (see special issue no. 32 of JNCI, 2004). The ramifications of AC likely extend well beyond these important concerns into a number of other diverse domains. As treatment advances have prolonged and improved the QOL of many people with metastatic disease, increased clinical and empirical attention has been directed to their psychosocial concerns. Of note, much

Table 1. Adaptive Tasks Faced by Individuals Living with Advanced Cancer

Physical and medical challenges

- Management of physical symptoms and side effects (e.g., pain, fatigue)
- Dealing with constant or changing treatment schedules
- Accepting stable disease as a desirable outcome of treatment
- Deciding to transition from curative to palliative care

Psychological challenges

- Coping with uncertainty and unpredictability
- Lack of control
- Fear of dependency
- Progressive losses in functional ability
- Maintenance of valued life goals
- Fear of death and suffering
- Balancing hope with realistic preparations for the future
- Management of complex emotions
- Unmet informational needs

Interpersonal challenges

- Communicating with friends and family about illness and death
- Social isolation and lack of emotional or instrumental support
- Concerns for loved ones
- Maintaining adequate communication with the medical treatment team

Spiritual and existential challenges

- Making sense of and accepting the cancer diagnosis in the context of spiritual beliefs
- Finding meaning in one's life and death

Practical concerns

- Knowing when and how to seek home help, transportation assistance, or other services
- Managing financial and legal affairs

of the existing research has been conducted in Europe, Canada, or Australia, where the health care context is quite different from that of the United States. Most of the research outlining adaptive tasks is also qualitative and based on semi-structured interviews with convenience samples of patients. Drawing from this small research base and our own applied experience in this area, we discuss some of the myriad demands faced by individuals with AC. Table 1 displays a summary of these adaptive tasks.

Physical and medical demands. The most common physical challenges of AC are the management of physical symptoms and side effects of treatment, most frequently pain and fatigue. Fatigue and sleep disturbance are experienced by a majority of patients with advanced disease,[5] and over half report pain at some point in the cancer trajectory.[6] Fatigue is the symptom that patients report to be the most distressing and to interfere most with daily life,[7] but pain and fatigue often co-occur. Both pain and fatigue can be side effects of therapeutic intervention or the result of the biologic effects of the cancer, and the prevalence of these symptoms is higher in palliative settings and during end-stage disease.[7,8]

Depending on the nature of the cancer, the sites of metastasis, and the treatments administered, physical symptoms might also include sexual dysfunction, incontinence, neuropathy, infertility, dyspnea, cognitive impairment, hair loss, constipation or diarrhea, nausea, loss of appetite, fractures, or itching.[5] Controlling these symptoms can be centrally important to many patients' QOL,[9] yet 63% of patients in one study described their symptom control as insufficient and ineffective.[10] The experience of symptoms that result from the primary cancer might be distinct from negative side effects of treatment, and physical symptoms of metastases might be different still. Indeed, some patients with AC report that they become hypervigilant to signs of further metastases, interpreting every mysterious ache or memory lapse as an indication of advancing disease.[9]

Any difficulty in managing physical symptoms is of critical importance, as people with AC report that their perception of physical well-being powerfully affects their ability to feel meaningfully engaged with life and to maintain hope.[9,11] Obviously, if someone is relentlessly nauseous, in pain, or crippled by fatigue, the goal of living well becomes secondary to ridding oneself of the symptom.

Among those with AC, constant treatment regimens can become burdensome. Depending on the status of their disease, people with AC may cycle through a series of different treatments and experimental drugs, such that they are constantly adapting to distinct side effects and schedules. The continuous nature of treatments and the need to adjust one's schedule to accommodate them may lead patients to feel dominated by their disease.[12] In addition to undergoing treatments, people living with AC may have frequent appointments for tests and scans to determine whether treatments have been successful or whether the disease is progressing. These evaluations, as well as the subsequent period of waiting for results, may be accompanied by acute anxiety and distress.[12] Due to the incurable nature of many ACs, patients may need to accept stable disease as a desirable outcome of treatment, a reality which often requires patients to disengage from goals of shrinking the tumor or eradicating the disease.

A related difficulty among those with AC is the transition from curative to palliative care, which may be accompanied by hopelessness, a sense of failure, or feeling that one has been abandoned by the medical team.[13] A number of factors are implicated in the difficult decision to make this transition, including the recommendation of the oncologist, the preferences of the patient and his or her family, potential side effects of treatment, patient age, time since diagnosis, and other contextual life variables such as having children at home and holding particular spiritual beliefs.[14–16] Though most patients prefer to be involved in this decision, greater patient participation in the decision to terminate or pursue additional curative treatment is associated with increased anxiety, at least temporarily.[17] Failure of curative treatment may also lead patients with AC to experience self-blame or regret about their treatment decisions.[18]

Psychological demands. Individuals with AC often find that they must learn to cope with uncertainty and unpredictability.[5,15] Granted, life is unpredictable regardless of whether one has been diagnosed with AC, but living with Stage IV disease harshly exposes this uncertainty. Patients with AC often report that they have "good days and bad days" characterized by great variability in their sense of physical and psychological well-being. These fluctuations may not be adequately captured by existing research designs, and as a result their disruptive impact on a patient's ability to plan for the future is not fully understood. The inability to predict how one will be feeling or to make social commitments or travel plans can be frustrating, restrictive, and isolating. For many patients with AC, the only solution to managing this unpredictability is to learn to make the most of good days (or hours) and to allow oneself flexibility on bad days.

Lack of control is another common complaint of adults living with AC,[19] to which patients may adapt by staying abreast of their treatment and progress, refocusing their efforts at control on those things in life over which they actually have control, relinquishing control to their medical treatment team, or pursuing alternative therapies such as guided imagery which give them greater sense of control over their illness. Adopting an approach of living "one day at a time" can also help people with AC to feel more in control of the present and less anxious about the future.[20]

Another common psychological concern revolves around issues of dependency and autonomy. Patients often fear becoming helpless and unable to care for themselves, and anxieties about becoming a burden to loved ones are common.[21] In one qualitative study, men with AC reported that their most important concern was being able to do things for themselves,[9] and the progressive loss of one's ability to perform role functions or activities of daily living is often met with feelings of futility and worthlessness. Depending on the rigidity of existing dyadic or familial roles, these issues may become especially challenging. For example, a father or husband may resist being dependent on his child or wife if that challenges the existing dynamic, and asking for help from parents may be particularly difficult for a young adult just establishing her independence. Rehabilitation for AC patients to preserve or recover functionality and prevent further decline has received little attention to date, although it may nourish hope and self-efficacy among this population.[22] Patients may also need to learn how to ask for and accept help from friends and family, to reframe their expectations for themselves, and to prioritize activities so that they can devote energy and physical resources to doing those things that are most important to them.

A related task of adapting to AC involves the maintenance of short-term and long-term goals. People with AC find it important to preserve daily plans and projects in order to feel autonomous and engaged with life.[9] Short-term goals can provide a structure that helps patients to maintain a sense of normality and routine,[20] whereas long-term goals can foster a sense of hope, generativity, and purpose in life.

In addition to fears of dependency, individuals with AC face a number of other specific fears, including fear of the process of death, of suffering, and of being alone.[5,15,23] Voogt and colleagues[15] reported that 40% of a sample of 105 patients with advanced breast, lung, and other cancers experienced fear of death at times and that 15% feared suffering. Indeed, as Osse[5] reported, patients' fear of pain can be more distressing than the pain itself. In working clinically with AC patients regarding death anxiety, it may be helpful to clarify the specific nature of an individual's fears of death, whether the underlying concern is a fear of unmanaged pain or suffering, of being alone when death comes, of leaving loved ones behind, or another specific concern.

The task of balancing hope with realistic preparations for the future is another critical undertaking faced by those with AC. For many patients, hope is dynamic and fragile, and the experience of "swinging, often in the same day, from hope to despair,"[12] is common.[11,12] Some patients describe this as "living while dying,"[9] of planning for the worst-case scenario while hoping for the best. Clinicians may want to explore with patients the wide spectrum of hope and what specifically they are hoping for, whether it is a miracle cure, surviving long enough to attend certain special events, finding meaning in life, achieving an important goal, enjoying the remainder of one's life with friends and family, managing symptoms and remaining comfortable, or having a peaceful death.[20]

Living with AC involves the management of complex and intense emotions. In addition to fear and hope, these can include anger, despair, guilt, and shame.[5,11]

Whereas some patients experience high levels of negative emotion, a more common emotional experience might include feeling less positive emotion and pleasure in daily life.[5,15] On the other hand, we have observed clinically that some individuals experience intense emotional blends of negative and positive emotions, such as poignant or bittersweet emotions accompanying the awareness that time with one's family is limited and precious.

Finally, patients with AC report many unmet informational needs, including the need for information about nutrition and complementary medicine as well as such sensitive topics as euthanasia, living wills, and hospice.[15] Discomfort seeking or absorbing this sensitive information may result in heightened distress and fear of what is unknown as well as failure to adequately prepare for the inevitable.

Interpersonal demands. Communicating with family and friends about one's illness and death is a critical adaptive task faced by individuals with AC. Patients may have difficulty socializing with acquaintances and even close friends and family members, some of whom either dramatize or minimize the patient's situation.[5] Some people may find attention to and questions about health undesirable and intrusive. Another common experience is the feeling that other people do not want to talk about one's illness and that inquiries after one's health reflect a sense of social obligation rather than genuine interest and concern. Although patients may recognize that this discomfort stems from fear or ignorance about how to be supportive, such interpersonal experiences can be frustrating and hurtful nevertheless.

Some patients may lack a confidant with whom to share emotions and fears and may not feel adequately supported or understood. Another social concern that is commonly reported by those with AC involves dealing with isolation and loneliness. This isolation can arise from feeling that others are not willing or able to be emotionally supportive, from the loss of role functioning and ability to work or socialize outside the home due to physical symptoms, from depression, or from feeling forsaken and disappointed by close friends or family members that one expected to be more supportive.[5] For people diagnosed with rarer cancers for which there is limited public awareness, lack of contact with others who have personal experience with the disease can also be isolating.

Patients with AC commonly experience considerable worry and distress about how their loved ones will cope when they are gone. This fear may be particularly powerful if a patient has young children or others who are dependent on him or her or if the patient is unable to express these concerns freely or is unsure of how to broach the topic with children, spouses, or family members. Therefore, a family member or friend may need to initiate these conversations and provide reassurance that he or she is open to such dialogue. Acknowledging these issues when there is adequate time to write letters or prepare other keepsakes for loved ones may provide families with additional strategies for managing fears of loss.

Difficulties may arise within families if there are conflicting attitudes or degrees of openness about cancer. For example, if family members are not willing to acknowledge the severity of the disease and insist on remaining optimistic about "beating the disease," patients may feel pressure to protect their family from the reality of their fears and suffering. In other situations, caregivers feel protective and may request that prognostic information be withheld from the patient. Even if both are willing to acknowledge the serious nature of the illness, it is common for patients and caregivers to want to protect the other and to worry about how the other will handle conversations about end-of-life issues or about their own fears and emotions. Individuals with AC and their caregivers may also feel pressure to be positive and to enjoy their remaining time together and may be reluctant to engage in difficult conversations. Consequently, patients may not have an opportunity to talk openly with their loved ones about death and dying despite mutual recognition of the serious facts,[24] a missed opportunity that some bereaved caregivers later regret. Clayton, Butow, and Tattersall[25] recommend that health care practitioners be open and consistent in discussions with families coping with AC and have separate conversations with patients and caregivers if possible so that each can express his or her unique concerns and ask questions without worrying about the others' reaction.

These communication issues highlight another group of concerns unique to AC, as individuals with metastatic cancer may have different experiences of the medical system and interactions with practitioners than patients being treated for early-stage cancer. At the time of diagnosis and treatment decision-making, patients may feel intensely supported by their oncology team, but as time passes this intensity of care and attention can diminish. People with AC may feel as if their oncologists are disappointed in them when curative treatment fails. In addition, the need for ongoing treatment, especially experimental regimens or treatment in a large teaching hospital, may mean that patients are not followed by the same medical staff for the duration of their treatment. As a result, continuity of care may be compromised, and patients may have difficulty building trust and rapport with each new practitioner. Another potential consequence of a changing treatment team is that the patient might experience increased responsibility for communicating his or her needs, preferences, and medical history to the treatment staff, an experience which may be anxiety-provoking or frustrating.

Much literature has been devoted to issues around communication with physicians and patients' desire for prognostic information (e.g., refs. 25 and 26). There may be significant individual and cultural differences in preferences of the patient and family. For example, in some Korean families, caregivers believe that diagnostic and prognostic information should be withheld from patients.[27] For the most part, however, research indicates that patients and families desire honest information about prognosis and treatment options and that they prefer that physicians balance truth telling with nurturing hope. Physician behaviors that encourage hope include being highly knowledgeable about the patient's cancer and indicating that pain and discomfort will be controlled, whereas acting anxious or uncomfortable, using euphemisms, or disclosing prognostic information to the family before the patient are viewed as detrimental to the patient's hope.[26]

Spiritual and existential concerns. For some patients with AC, religion and spirituality become important sources of comfort and social support.[9] Some may feel that the suffering and pain they are enduring will lead to spiritual rewards and sanctification.[23] Others may find their faith challenged by the diagnosis and may begin to question their belief system. For still others, religion and spirituality have never been important to them, and AC does not change this. Even if individuals with AC are not spiritual, many experience existential struggles as they strive to define the meaning of their life and make sense of their situation.[11] The literature on spirituality in AC is quite limited, although many individuals indicate that these issues are of vital concern. Aspects of spirituality described as important to patients include being engaged usefully and feeling capable of helping others, maintaining confidence in one's religion, finding meaning in one's life and death, and accepting the disease.[5]

Practical concerns. Practical issues can be a source of tremendous stress and strain for patients with AC and their caregivers. For example, many struggle with deciding when home help is needed and finding and accepting this assistance. Nearly half of 100 caregivers assessed by a social worker were characterized as "needing additional assistance" such as skilled home nursing, medical equipment, or help with transportation.[28] In one sample, professional help for activities of daily living was available but not always readily accepted, as the experience of having different nurses rotating through one's home to perform hygienic care and other intimate tasks was considered "degrading, humiliating, and intrusive."[5] In this same sample, even when participants had home help, there was a universal concern that the home health aides might not be available when most needed, such as during the night or in case of an emergency.

Individuals with AC may also face a number of financial and legal issues. Because many people with metastatic cancer are unable to work, they may experience a decrease in household income at the same time that medical bills are mounting. In one study, inadequate medical insurance or ability to pay for medical care independently predicted psychological distress.[3] Thus, financial strain for patients and families is another burden that must be managed. Another task that many patients with AC experience as important and distress-provoking is the need to get one's financial and legal affairs in order in the event of one's death.

To summarize, people living with AC may face diverse and simultaneous concerns that can seem overwhelming to the patient and support network and inadequately addressed by traditional oncology services. Increased awareness of these concerns by health care providers may result in more comprehensive and sufficient support during AC. Demands vary across individual patients and across the disease trajectory, so an individualized approach is warranted.

4.0. WHAT IS SUCCESSFUL ADAPTATION TO ADVANCED CANCER?

The extant literature on patients with metastatic cancer focuses almost exclusively on two indicators of psychological adjustment: depression/distress and QOL. Reports of the prevalence of emotional distress among individuals living with AC vary depending on the method of assessment and the nature of the sample.[29] Several large studies and literature reviews estimate the prevalence of depression in AC to be approximately one-quarter to one-third of patients.[29–35] Studies using self-report instruments generally report higher prevalence rates than those using structured psychiatric interviews to diagnose depression,[29] and rates may be inflated if measures include somatic symptoms of depression (e.g., fatigue, insomnia).[36] Estimates based on the perceptions of caregivers or physicians may also inflate the prevalence of distress, as one study based on palliative care social workers' assessments of patient functioning found that 63% of patients were anxious and 54% were depressed.[28] In general, these findings suggest that although distress and depression can be significant in samples with AC, they are not universal. In fact, one noteworthy comparison study concluded that the prevalence of psychiatric disorder in women with early and advanced breast cancer was equal.[33] In this study, 37% of 303 women with early-stage breast cancer met criteria for mood disorders, compared to 31% of 200 women with metastatic breast cancer.

In the medical literature, QOL is a standard indicator, often in the context of ascertaining whether biomedical treatments or side effects impair QOL or whether QOL is an independent predictor of survival. Quality of life, an individual's sense of well-being based on his or her current experience of life as a whole, overlaps

Table 2. Correlates of Poor Adaptation in the Context of Advanced Cancer

- Severity of physical symptoms (especially pain) and poor functional status
- Poor prognosis and perceived life threat
- Younger age
- Less satisfactory perceived social support
- Repression of emotional experience or expression
- Low dispositional optimism

considerably with distress, as depression and anxiety account for most of the variance in QOL.[37] However, QOL instruments often include indices of physical well-being and social role functioning in addition to psychological well-being. Growing evidence supports the prognostic significance of self-reported QOL in the context of AC.[38–40] Investigators have argued that this predictive relationship reflects patients' awareness of their health status that is not captured by traditional prognostic markers,[40] although the possibility remains that QOL has a causative impact on survival.[38]

Although measures of depression and QOL provide critical information about the psychological status of AC patients, we argue that a more nuanced view of adjustment could guide clinical practice and stimulate research. Rather than an acute event to which one might adapt and move beyond, living with AC is a dynamic and evolving stressor. The work of adjusting to life with AC continues until one's death, and patients' success at accommodating the losses, life disruption, and existential concerns that accompany AC will vary over time. Perhaps a constructivist approach to adaptive survivorship can provide insight into additional ways to define and measure well-being in this population. Constructivism views individuals as motivated to adapt one's self-concept to disruptions in the life narrative and to find personal meaning in such losses.[41] Indeed, the experience of finding meaning or benefit in living with AC is commonly reported and often coexists with distress or depression.[11,42] Are survivors living with AC who find existential meaning and purpose in their experience but continue to experience high levels of sadness well-adjusted? What about patients who report no distress related to their AC because they do not acknowledge the severity of their diagnosis? To determine whether patients with AC are managing the adaptive tasks laid out in the preceding section successfully, it may be necessary to assess both psychological distress and dysfunction as well as more positive outcomes, such as a sense of personal strength and self-efficacy, spiritual well-being, and the acceptance and integration of one's cancer experience into a meaningful life narrative. The next section and Table 2 summarize the small literature on correlates of adjustment to AC.

5.0. CORRELATES OF ADJUSTMENT

Medical and prognostic variables. As described briefly in the section on medical adaptive tasks, physical symptomatology and health status are often found to be strongly correlated with depression and QOL.[3,31,32,34] Pain and fatigue in particular are associated with higher levels of distress.[3,15] In women with metastatic breast cancer, both pain intensity and frequency have been correlated with depression and mood disturbance.[43] However, as many of these studies are cross-sectional, it is not possible to determine whether pain and fatigue play a causal role in producing distress or whether depressed patients are more likely to report physical symptoms. Most likely, the relationship is bidirectional, where pain and fatigue contribute to helplessness and depression, and negative emotions exacerbate physical symptoms.

To the extent that more advanced disease is accompanied by greater physical morbidity, prognosis is likely to influence QOL. In addition, subjective perception of the severity of one's illness may be particularly important. Magnitude of perceived life threat has also been associated with QOL, where greater life threat is related to traumatic stress symptoms and impaired QOL independent of stage of disease.[44] However, a study of 200 AC patients in their final weeks of life demonstrated that the prevalence of depression was three times greater among the 10% of patients who denied awareness of their terminal prognosis and foreshortened life expectancy.[45] Perhaps full prognostic awareness is adaptive for some people with AC and detrimental for others, or especially critical in the final months of life, but these moderated relationships have not yet been examined.

Demographic and social contexts. The demographic variable that has most commonly been linked to adjustment is patient age, such that older patients generally report less distress and greater well-being.[15,37,46–48] Older patients may have fewer competing demands on their time and resources if they are retired and have fewer caretaking responsibilities. In addition, illness in old age is more developmentally normative and consistent with expectations about how one's life will go, so a diagnosis of AC may be less distressing to this group. No evidence has been found for gender differences in adjustment to AC.[49] Research on ethnic minorities is limited, but preliminary data suggest that significant disparities may exist in treatment and support services provided as well as in adjustment.[50,51] The concurrent experience of other life stressors may also create a context predictive of poorer adjustment if one's intrapersonal or interpersonal resources become taxed.[52]

A patient's social context may be associated with their ability to adjust to AC, and investigators have examined different aspects of social support. For example, one study demonstrated that greater perceived social support was related to lower distress, even after controlling for physical health status.[3] In another study, having more people in one's social support system was correlated with less mood disturbance, but only among patients who had undergone high levels of previous life stress.[52] Perhaps quantity of social support is less important than the perceived quality of support, such that the number of people in one's network is less predictive than whether a patient perceives that support is available when needed. Marital status and quality have also been examined, and a study of metastatic breast cancer patients revealed that partnered women did not differ from single women in the amount of mood disturbance reported once household income was statistically controlled.[53] This is consistent with other work suggesting that marital status alone is not predictive of adjustment.[49] In this same study, partnered women were less distressed when their relationship was characterized by relatively high cohesion–expression and conflict, which the authors interpreted as evidence of the benefit of open engagement and communication.[53] In direct contrast to this finding, a study of AC patients on hospice care and their primary caregivers found that openness about feelings was linked to greater anxiety and depression.[54] Again, the effect of open communication in important relationships may be moderated by the timing of assessment and severity of disease, where openness is associated with less distress when the patient has the physical resources to actively engage in these conversations but correlated with more distress during the last weeks of life. In addition, the cross-sectional nature of these studies does not allow for causal inference, as distressed families may also be more emotionally expressive at the end of life.

Personality variables. There are relatively few investigations of the relations between personality attributes and adjustment in patients with AC, but preliminary evidence suggests that the dispositional traits of emotional expressiveness, low chronic anxiety, and optimism may predict psychological well-being. Emotional regulation styles typified by conscious suppression or lack of awareness of affect appear problematic for patients with AC. For example, high dispositional emotional control (i.e., suppression) was associated with greater mood disturbance in a study of 101 metastatic or recurrent breast cancer patients.[55] Similarly, a study by Weihs and colleagues[56] demonstrated that AC patients who are habitually unaware of their emotions report more negative mood states than those that are less repressive. In addition, the individuals in this sample who reported the most mood disturbance were those that were both emotionally constrained and dispositionally anxious, suggesting that the combination of repression and negative affectivity may be especially detrimental to well-being in the context of AC. In another sample of breast cancer patients, repression was not associated with high levels of self-reported anxiety and distress, but women high in repression experienced the same physiological patterns as individuals reporting high levels of anxiety (i.e., flattened diurnal cortisol slopes).[57] This finding may indicate that although emotionally inhibited individuals may be unaware of their emotions, they may suffer the same maladaptive physical health consequences as chronically anxious patients.[57] Overall, these findings suggest that individuals who constrain the expression or experience of their emotions may have difficultly adapting successfully to a diagnosis of AC, and the work of Giese-Davis and colleagues[57] highlights the methodological challenge of assessing these individual differences.

Optimism has received support as a predictor of positive adjustment in early stage cancer (e.g., ref. 58), and this dispositional tendency to expect positive outcomes has also been found to predict well-being and enhanced emotional functioning in patients with AC.[46,59] There is also interest in whether individuals with AC are more or less optimistic than cancer patients with less severe disease. Preliminary investigations have yielded conflicting results regarding this association. Miller *et al.*[46] found that patients with AC reported greater levels of optimism than did cancer patients in other studies; however, other research suggests that levels of optimism do not correspond to disease stage.[59] Gotay *et al.*[59] found that optimism was correlated with enhanced emotional functioning and less depression across all stages of cancer, indicating that this personality characteristic may operate similarly throughout the course of cancer.

Coping processes. Although the effectiveness of particular coping strategies has been studied extensively in cancer patients in general, specific coping processes may be differentially related to adjustment among AC versus earlier-stage cancer patients, as individuals with AC are negotiating distinct issues. For instance, if remission of cancer is no longer a feasible goal, efforts may be focused on symptom management, grappling with end-of-life issues, and maintenance of daily functioning and social connections. Additionally, each of these goals may necessitate different coping strategies. Social and existential goals may call for strategies such as seeking social support whereas managing pain may require a problem-focused approach such as requesting a consultation with a pain specialist.

Limited research addresses the mutability of coping in the context of AC. One study sought to demonstrate how coping patterns might change throughout AC by assessing use of coping strategies every 3 months in a sample of metastatic melanoma patients.[49] Any assessment completed within the last 12 months of life was analyzed. Contrary to expectation, results indicated that behaviors aimed at problem-solving such as "seeking more information about the situation" increased significantly over the final year of life. Coping through distraction and avoidance did not change, but note that those variables had very low internal consistency reliability. In another study involving a small group ($n = 10$) of AC patients entering a phase I trial, Sherliker *et al.*[60] found that choice of coping strategies did vary depending upon circumstances. Specifically, patients with AC sought more social support when experiencing an acute health event (i.e., receiving treatment in the hospital) than when they were not. Additional research is needed to clarify how coping strategies might shift throughout cancer course.

Research examining the relationship between coping and adaptation is also limited. Not allowing oneself to express negative feelings (i.e., anger, anxiety, and depression) has been associated with greater mood disturbance.[55] Conversely, a determined attitude focused on overcoming cancer has been associated with less mood disturbance.[55,60] The effectiveness of this attitude, labeled "fighting spirit," suggests that active attempts to manage one's disease may be beneficial.

In another sample of mixed cancer patients, attempting to avoid or escape the stressor (i.e., cancer) and blaming oneself for aspects of the disease predicted increased distress over time.[46] However, endorsement of the statement "I act as though it [cancer] hadn't ever happened," was correlated with positive daily mood in a small sample of patients with AC.[60] Avoidance has also been associated with other aspects of adjustment such as greater satisfaction with doctor–patient communication in patients with AC.[61] Notably the assessment instruments used by Miller and colleagues differed from these other studies in their measurement of behaviors such as "avoided being with people in general" that might indicate heightened distress or be maladaptive for other reasons (e.g., socially). Although the above results indicate that avoidance may be an effective coping strategy in AC, caution should be used when interpreting these findings, as there are a limited number of studies in this area and no consistent or standardized measurement of avoidant strategies. Nevertheless, in AC, putting cancer out of one's mind occasionally may provide a much-need respite from the demanding task of adapting to terminal illness, allowing survivors to function at a higher level and to enjoy life more than might be possible if they were constantly engaged with the work of adjusting to the disease.

Emotional expression, active coping, and avoidance, have all predicted positive adjustment to AC. Although seemingly counterintuitive, these results may indicate that the multifaceted issues faced by patients with AC call for diverse coping strategies. Perhaps it is best to ignore or avoid those aspects of the disease that seem overwhelming and immutable, to employ problem-focused strategies in managing controllable practical and medical issues, and to express one's emotions about uncontrollable concerns to facilitate social support and discovery of meaning. Thus, a flexible coping style allowing an individual to choose an appropriate coping strategy based upon the stressor, current health, and available psychosocial resources may be predictive of adjustment to AC. To address these questions, research will need to move beyond cross-sectional "snapshots" of coping to an experience sampling approach or other methodologies that capture the intraindividual variability in coping processes and adjustment.

Spirituality. A terminal illness prompts end-of-life concerns that may be influenced by one's spiritual, religious, or after-life beliefs. Spirituality, often described as a universal connection to the transcendent and search for meaning in life that need not be associated with a divine figure,[62] appears to have a protective effect in some psychological domains for patients with AC. Self-described spiritual patients endorse less end-of-life despair, less desire for a hastened death, and more positive QOL,[63–65] but not less depression or anxiety than patients who do not identify themselves as spiritual. Patients with AC who enroll in Phase I clinical trials endorse more spirituality than those who do not,[64] suggesting that spirituality might influence hope or the desire to continue treatment despite advanced stage disease. Although not predictive of less depression, spirituality has been shown to moderate the effects of depression on desire for a hastened death. For instance, patients with AC who were depressed and low in spirituality indicated a greater desire for a hastened death than did patients with AC who were depressed but also identified themselves as spiritual.[66] Importantly, the relationship between spirituality and well-being exists even after accounting for individual differences in after-life beliefs,[65] indicating that spirituality's influence on adjustment is not simply driven by a belief in life after death.

Summary. In summary, research identifying correlates of adjustment in the context of AC is limited. The existing literature suggests that troubling physical symptoms, especially pain and fatigue, are associated with compromised psychological well-being. Evidence also suggests that older patients experience less distress than younger individuals with AC, that greater perceived social support predicts positive adjustment, and that optimism may be protective and inhibition of emotional expression deleterious for AC patients. Findings are more limited and inconclusive for the predictive utility of other demographic variables, emotional expressiveness in interpersonal relationships, coping processes, and spirituality. Finally, although this review has focused on psychosocial predictors of psychological adjustment in AC, the examination of psychosocial predictors of mortality and disease progression is gaining empirical attention (e.g., refs. 56 and 57) and provides an opportunity to test biopsychosocial models of metastatic disease.

6.0. PSYCHOSOCIAL INTERVENTIONS FOR SURVIVORS WITH ADVANCED CANCER

To date, a limited number of psychosocial interventions for AC patients have been rigorously tested. These include supportive-expressive therapy (SET[67–70]), group cognitive–behavioral therapy,[71–73] and written emotional expression.[74] SET involves weekly 90-minute therapy groups led by experienced mental health practitioners, and the goal is to create a supportive environment and encourage the expression of cancer-related emotions and difficulties. Therapy sessions are relatively unstructured, with discussion organized around themes such as fears of death and dying, reordering life priorities, improving support from friends and family, and integrating a changed self.[68] SET may also include a hypnosis or relaxation component.[69,70] This therapeutic approach garnered considerable scientific scrutiny and media attention after a randomized controlled trial conducted by Spiegel and colleagues demonstrated an estimated 18-month survival benefit for metastatic breast cancer patients who participated in the treatment groups compared to the no-therapy control condition.[70] This finding has not been replicated,[69] although other trials of SET indicate a decline in mood disturbance, the perception of pain, and traumatic stress symptoms related to breast cancer among women assigned to participate in SET groups[68,69] but no effect on health-related QOL as assessed by Bordeleau and colleagues.[67] In addition, it has been demonstrated that the women who were most distressed at baseline were more likely to benefit from the intervention,[68,69] though SET may not improve mood in the year proximal to death.[68] Thus far, randomized controlled trials of SET for AC have been limited to women living with advanced breast cancer, and its effectiveness for patients with other ACs has not been demonstrated. Although the themes discussed in SET are common to most patients with metastatic disease, the generalizability of effects of an intervention focused on social support and emotional expression has not been demonstrated in more rare, aggressive, or stigmatized cancers, such as advanced ovarian or lung cancer.

The other psychotherapeutic approach that has been investigated in the context of AC is cognitive-behavioral therapy (CBT). Like SET, this therapy has generally been administered to advanced breast cancer patients in weekly small group sessions. However, CBT interventions for AC patients have generally been more structured and didactic, incorporating the use of cognitive restructuring, behavioral relaxation and communication skills training, and weekly homework exercises in addition to the expression of feelings and the development of group support.[72] In addition, CBT groups tend to be briefer in duration than the more open-ended SET groups, ranging from 8–35 weeks.[71,72] Trials of CBT have demonstrated short-term improvements in mood and self-esteem in the treatment group relative to a no-treatment control group, but these gains were not sustained at 3- or 6-month follow-up.[71,72] In addition, no survival benefit of CBT groups has been reported.[71,73]

Several barriers to implementing group therapy interventions among patients living with AC have been described, largely recruitment and compliance difficulties resulting from patients' compromised health. Medical treatment schedules may interfere with therapy sessions, and patients may have trouble attending sessions, actively participating, or completing assessments due to physical symptoms.[67] As a result, it may be difficult for those patients who might benefit the most from group-based, in-person psychosocial interventions (i.e., the most ill and distressed; ref. 69) to participate in them.

Emotionally expressive writing is an intervention that has been considered as a potentially cost-effective and minimally invasive psychosocial treatment for AC patients. In this paradigm, participants are assigned to write about either their deepest thoughts and feelings about their cancer or to write about a neutral control topic (e.g., a different health behavior) for 20 minutes across four writing sessions. Like SET, expressive writing also allows individuals living with AC to confront cancer-related thoughts and feelings, put their experience into words, and integrate cancer into their life story. To date, one pilot trial of expressive writing has been conducted in AC patients. This trial, conducted in a sample of metastatic renal cell carcinoma patients enrolled in a clinical vaccine trial, demonstrated no intervention effect on perceived stress or mood disturbance but did suggest that patients who wrote about their cancer experienced better sleep quality and greater vigor compared to the control group.[74] These preliminary findings are promising and suggest a potential therapeutic alternative in which AC patients could participate from their homes as their health and treatment schedules allow. Certainly, expressive writing and other psychosocial interventions designed with the concerns and limitations of AC survivors in mind warrant further investigation. Although an eventual decline in health and QOL may be inevitable for most AC patients,[67] psychosocial interventions that effectively slow this decline or encourage positive psychological growth hold significant promise for facilitating adaptation to life with AC.

7.0. FUTURE DIRECTIONS FOR RESEARCH AND PRACTICE

Clearly, the face of advanced malignant disease is evolving along with the development of life-prolonging and palliative therapies for AC as well as early detection strategies to limit the incidence of metastatic cancer. We have reviewed the existing literature on adaptation to AC, highlighting those aspects that are unique to patients living with incurable metastatic cancer. Future research is warranted to determine how clinicians can best help patients manage the adaptive tasks described in this chapter. We turn now to potential avenues for future research and clinical practice.

Additional qualitative and quantitative research will be necessary to identify the physical, psychological, social, spiritual, and practical concerns most central to patients living with AC. As these concerns are likely to vary across cancer site, by demographic and sociocultural context, and across the cancer trajectory, it will be important to capture the heterogeneity of the AC experience. As knowledge of the adaptive tasks that characterize life with AC accrues, the development of standardized measures to assess these concerns and the associated emotional reactions would allow researchers to compare different AC samples and to determine the challenges that are most distressing to each population.

Research highlighting the positive aspects of adaptation to AC will also expand our understanding of the psychosocial experience of patients living with cancer. Though distress and life disruption may be common, investigations of early-stage cancer patients indicate that severe negative impact and perceived threat related to one's illness can catalyze profound positive change and personal growth.[42] It will be important to examine whether this phenomenon also occurs in the context of AC. In addition to assessing distress and QOL, future research will need to examine the dialectical relationship between these adverse outcomes and more positive outcomes, such as discovery of meaning and strengthening of interpersonal relationships.

To date, most research on AC has been cross-sectional. As a result, researchers may not have access to the dynamic challenges and adaptive processes unfolding across the cancer trajectory. Among patients living with advanced disease, their reports of physical and psychological well-being may differ from day to day, depending on how well side effects and symptoms are managed, their latest test results, and a range of other variables. Experience sampling methodology would allow investigators to capture these dynamic fluctuations and to identify proximal predictors of QOL and distress. Longitudinal research designs will also be necessary in order to monitor adjustment over time and to examine causal relationships between coping and interpersonal processes and psychosocial outcomes. Such longitudinal investigations would provide insight into the predictors of adjustment to AC that can guide intervention and clinical practice.

There is also a need for the development of clinical interventions to maximize QOL and facilitate adaptation for patients living with AC. Future interventions should be (1) guided by both research and theory, (2) rigorously tested in randomized controlled trials across a range of ACs, (3) cognizant of the functional limitations of patients with AC, (4) targeted to individuals or cultural or diagnostic groups for which they are likely to be most efficacious, and (5) delivered to those patients that are most in need of and most likely to benefit from psychosocial intervention.

As evidenced by this review, the adaptive tasks faced by individuals living with AC are myriad, unique from those confronted by early-stage cancer patients, and inadequately targeted by existing clinical interventions. Research is needed to determine the optimal strategies for addressing these concerns and enhancing QOL for individuals living with advanced malignant disease.

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Part III

Secondary Prevention

Chapter 13

Restoring Emotional Well-Being

A Theoretical Model

Robert W. Lent

1.0. INTRODUCTION

Surviving cancer does not just mean recovering one's physical health and adding theoretical years back to one's life expectancy. It also entails coping with the many extra-physical (e.g., emotional, social, occupational, financial) issues that typically accompany—and may extend well beyond—the acute experience of cancer diagnosis and treatment. Indeed, in a recent survey of self-identified cancer survivors (most of whom had received a cancer diagnosis more than 2 years prior to the survey), 40% indicated that their life was still affected "more than a little" by cancer, 53% replied that it was harder dealing with their emotional than their physical needs, 60% experienced problems in a close relationship, 32% reported job disruptions or loss, 72% reported suffering with depression at some point in their recovery, and 70% felt their physician had been unable to help with their nonmedical needs (see Wolff, this volume).

Such statistics underscore the findings of many quantitative and qualitative studies attesting to the significance of psychosocial and other nonmedical aspects of cancer survival. McKenzie and Crouch,[1] for example, poignantly described the existential, self-identity, and relationship challenges with which many cancer survivors contend, and Main *et al.*[2] documented the difficulties often encountered in work situations. A number of investigators have examined the occurrence of, or tested interventions to ameliorate, the psychological symptoms (e.g., depression, anxiety) or challenges to quality of life wrought by the cancer experience (e.g., Osborn *et al.*[3]).

This chapter focuses on one fundamental aspect of cancer survival: the emotional well-being of the survivor. After defining what I mean by emotional well-being, I will present a theoretical model suggesting how people generally restore their sense of well-being after it has been disrupted by stressful or traumatic life events, and discuss the implications of this model for research and the practice of secondary prevention with cancer survivors. I come to the topic of cancer survivorship via a general interest in psychological health and adaptation, including how people cope with adversity. This interest led to the recent development of integrative theoretical models of well-being maintenance and recovery.[4] Although these models were not aimed specifically at the cancer experience, this chapter will attempt to trace their potential relevance to emotional coping and well-being recovery in the context of cancer survivorship.

2.0. WHAT IS EMOTIONAL WELL-BEING?

In recent years, there has been a major shift in psychology toward the study of optimal human functioning and adaptive tendencies.[5] This "positive psychology" movement has been intended as a corrective to the field's long-term tendency to focus on ill-being and psychopathology rather than on well-being and positive adjustment. Part of this movement has involved a rekindling of earlier interest in what might be termed *hygiology*—that is, "locating and developing personal and social resources and adaptive tendencies,"[6(p.5)] even in the midst of distressing or abnormal life conditions.

The notion of hygiology implies that health can be defined in relative terms. For instance, different individuals faced with the same life-threatening physical illness may differ markedly in their psychological adaptation based, in part, on the strengths, resources, and coping methods at their disposal. Rather than focusing only on ameliorating psychological symptoms (e.g., anxiety, depression, anger) that they may experience, a positive psychology or hygiological response would be more concerned with how to bolster these individuals' positive coping tendencies and resources. Although the goals of reducing symptoms and increasing positive adaptation may draw on overlapping therapeutic strategies (and, indeed, the one process may partly enable the other), it is also reasonable to assume that a focus on restoring emotional well-being (i.e., enhancing positive adjustment) may profitably entail development of unique methods, compared to those involved only in mitigating worrisome symptoms.

2.1. Two Views of Well-Being

At this point, I should clarify what I mean by emotional well-being. Ryan and Deci[7] noted that the study of well-being in psychology emerged from two relatively distinct, though overlapping, philosophical perspectives: (a) the *hedonic* position, which views well-being in terms of the experience of personal happiness or the balance between positive and negative affect; and (b) the *eudaimonic* position, which holds that well-being involves the quest to achieve growth, purpose, and meaning in one's life. These two broad perspectives have given rise to two relatively distinct lines of inquiry. Specifically, the hedonic view has nurtured development of the literature on emotional or subjective well-being (SWB[8]), while the eudaimonic view has fostered the study of psychological well-being (PWB[9]).

There has been an evolving consensus that SWB consists of three components: life satisfaction (the tendency to evaluate one's life as generally happy or satisfying), the presence of positive affect (e.g., enthusiasm, interest), and the absence of negative affect (e.g., nervousness).[8] Findings indicate that these are interrelated, though relatively distinct, constructs (e.g., Lucas *et al.*[10]) that may function together as part of a complex well-being process. By contrast, PWB research focuses on person qualities that are assumed, on theoretical grounds, to reflect healthy functioning (e.g., sense of life purpose, positive relations with others, self-acceptance).[9]

Consistent with their differing theoretical and philosophical roots, factor analyses of SWB and PWB measures suggest that they reflect somewhat distinct underlying dimensions of well-being (i.e., happiness/SWB vs. growth/meaning[11,12]). At the same time, several aspects of PWB have been found to correlate highly with life satisfaction/SWB.[13] Ryan and Deci[7(p.148)] concluded that "well-being is probably best conceived as a multidimensional phenomenon" that includes aspects of both SWB and PWB.

While Ryan and Deci's conclusion is well-reasoned, it seems essential to take the next step—that is, to ask the question, *how* do SWB and PWB interrelate (i.e., what is the role of the one vis-à-vis the other)? To address this question, it may be helpful to consider a theoretical framework that encompasses both sets of factors and that offers testable hypotheses about how they fit together. In my theoretical view, SWB—and more specifically, satisfaction with one's life overall and with the central domains/roles of one's life—is the aspect of emotional well-being that deserves particular focus in mental health interventions. PWB is not treated as an alternative or co-criterion of well-being; rather it is seen as offering a central route to SWB. In particular, the resources (e.g., social relations) and methods (e.g., pursuing valued goals) that people use to bring meaning, purpose, and structure to their lives (PWB) also help to promote their emotional well-being, or happiness (SWB). (In the remainder of this chapter, I will use the terms emotional well-being as synonymous with SWB, happiness, and life satisfaction.)

2.2. SWB and Quality of Life

Before elaborating my theoretical position, I will pause to distinguish SWB from a related concept, *quality of life* (QOL). Although the terms SWB and QOL are sometimes used interchangeably, they do not necessarily reflect the same thing. Indeed, QOL is often used as a conceptual umbrella for a wide array of constructs and measures that reflect some aspect of physical, social, or emotional functioning.[14] From this perspective, SWB is one of several indicators of life quality; other examples include social support and adjustment, physical health status, and economic standard of living. This eclectic mix of QOL indicators may reflect the multidisciplinary roots of the QOL literature in sociology, medicine, and psychology.

Although the QOL construct is useful in its focus on numerous aspects of positive adjustment, it may come with excess conceptual baggage. In particular, its multiple meanings may sacrifice precision for breadth and confound emotional adjustment with other aspects of functioning and with socioeconomic status. These are considerable limitations. Purchasing power, for instance, should not be equated with mental or physical health; and physical disease does not necessarily imply emotional ill-health. It is useful to view the person (and his or her environment) along multiple dimensions, yet there is conceptual danger in blurring the distinctions among them or in reducing them all to a single aggregate index of functioning. In the remainder of this chapter, I focus on emotional well-being, or SWB, while also acknowledging the value of assessing other aspects of adaptation (e.g., psychological symptom status, adequacy of role functioning) as part of a more comprehensive picture of psychosocial adjustment during the course of cancer survival.

3.0. THE DISPOSITIONAL PERSPECTIVE ON EMOTIONAL WELL-BEING

It has been found that people tend to display fairly stable levels of SWB over time, especially when their life circumstances remain stable. For instance, Headey and Wearing[15] reported that life satisfaction and the experience of positive and negative affect each showed moderate levels of stability over 2- to 6-year periods. However, these three aspects of SWB were not set in stone: some individuals showed considerable change in them over time, and the occurrence of significant life events was found to explain unique variance in SWB beyond personality factors. Headey and Wearing offered a "dynamic equilibrium" hypothesis suggesting that situationally induced changes in SWB are likely to be temporary because stable (presumably genetically-based) person characteristics tend to return people to their baseline levels of affective experience over time. Consistent with this hypothesis, it has been found that the impact of many life events on the three indicators of SWB often diminishes within about 3 months for many persons,[16] and even many major life changes—both positive (e.g., winning the lottery) and negative (e.g., incurring a spinal cord injury)—tend to have a limited effect on life satisfaction over the long run.[17] However, life events associated with significant loss or chronic stress have the potential to diminish long-term life satisfaction, and there are substantial individual differences in emotional adaptation after such events.[18]

The dynamic equilibrium hypothesis implies that each person has a characteristic affective "set point." Just as a thermostat automatically adjusts ambient temperature to conform with a pre-set target, an affective set point would allow for some fluctuations about one's typical level of SWB—positive and negative life events may cause one's usual emotional temperature to rise or fall, so to speak. But over time, this perturbation somehow engages homeostatic emotional regulation processes that gradually bring SWB back to the person's normative set point. This hypothesis is associated with what may be termed the "strong nature view" of SWB. Such a view is supported by behavior genetic findings suggesting that a large portion of the variance in current and (even more so) long-term SWB is due to genetic factors.[19]

Advocates of the strong nature view have concluded that SWB is itself essentially a trait that is regulated through more or less involuntary biological processes. McCrae and Costa,[20(p.228)] for example, suggested that "happiness and the chronic emotional reactions that underlie it are probably best understood as reflections of enduring dispositions." Meehl[21] referred humorously to "cerebral joy-juice" and "basic hedonic capacity" (i.e., largely heritable properties that produce differential susceptibility to positive and negative emotions) and also offered an "old Wild West maxim" that "some men are just born three drinks behind"(p. 298). Likewise, Lykken and Tellegen[19(p.189)] argued that trying to be happier is likely futile and that long-term well-being is "determined by the great genetic lottery that occurs at conception."

So what does the strong nature, or behavior genetics, view of SWB imply about emotional recovery in the context of cancer survival? First, it suggests that cancer survivors have experienced a life event with the potential to significantly decrease their life satisfaction and typical positive affect (and to raise their characteristic level of negative affect), at least in the short run. Second, it implies that many, though not all, cancer survivors will tend to gradually return to their pre-cancer levels of SWB—in other words, emotional resilience (defined in terms of return to one's personal baseline) is normative. Third, it suggests that the emotional recovery process is mostly "a matter of time" and "letting nature takes its course." That is, SWB is likely to restabilize no matter what the patient does and in the absence of psychotherapeutic or pharmacological intervention.

3.1. Limitations of the Dispositional Perspective

When one considers that most people tend to be generally happy with their lives,[22] the notion of a more or less automatic return to a positive affective set point may not sound bad. However, there may be significant limitations to the strong nature view of SWB and its implications for mental health intervention (or nonintervention) with cancer survivors. In particular, although traits clearly account for a substantial portion of the variation in SWB, they do not explain all of the variance, and mere documentation of trait-SWB relations does not illuminate the mechanisms or processes through which traits may be causally linked to SWB.[23] Indeed, other evidence suggests that SWB is multiply determined, that non-trait person and environment factors play important roles in affective regulation, and that some people experience quite substantial and long-term changes in SWB over time (see Lent[4] for a review). Thus, there is no guarantee that people will effortlessly or invariably return to a satisfying affective set point if left to their own devices. Moreover, relatively brief psychosocial interventions have been shown to promote SWB, both at posttest and 6–18 months later, albeit in nonclinical adult samples.[24–26] Such findings question Lykken and Tellegen's[19] conclusion that happiness cannot be modified.

Although there is need for more research on the long-term effects of the cancer experience on SWB per se, available evidence suggests that many individuals face continued emotional challenges long after their cancer was detected and treated[1] (Wolff, this volume). And, for some individuals, the cancer experience may be akin to other life traumas (e.g., involving loss of valued life roles or resources) that have the potential to provoke long-term change in SWB—as it were, to recalibrate affective set point in a negative direction. On the other hand, it is somewhat reassuring to note that many cancer survivors compare favorably to healthy controls or population norms on measures of well-being several years after being diagnosed and treated.[27–29] Yet, even if naturally occurring psychobiological processes help to restore emotional equilibrium after major upheavals, it is still possible that such processes can be hastened and augmented by well-designed interventions, thereby reducing periods of acute emotional distress and mitigating unnecessary suffering.

4.0. COGNITIVE, BEHAVIORAL, AND SOCIAL CONTRIBUTORS TO EMOTIONAL WELL-BEING

If a trait perspective tells only part of the story of SWB, then what added elements are needed to complete, or at least expand, the tale? My reading of the SWB literature suggests that traits function along with, and partly through, a variety of cognitive, behavioral, and social variables—and that study of these additional determinants may promote a more comprehensive understanding of SWB under both normal and particularly stressful life conditions. Moreover, such variables are seen as largely mutable and open to self-directed and environment-facilitated change efforts. They, therefore, may be cast as acquirable skill sets, strategies, and resources that can inform interventions to help people recover their SWB in the aftermath of psychologically taxing experiences, such as cancer diagnosis, treatment, and its side effects.

4.1. Cognitive Variables

Three types of cognitive variables have received a good deal of focus in the well-being literature: (a) beliefs about personal control, (b) future outcome expectancies, and (c) goal mechanisms. Control beliefs involve people's convictions about the extent to which they can control important aspects of their lives. Future outcome expectancies refer to people's beliefs about the future conditions of their lives (e.g., anticipation that positive or negative events will occur). Goals may be defined as "consciously articulated, personally important objectives that individuals pursue in their daily lives"[30(p.915)]; goals vary in content and salience from person to person.

Bandura's[31] social cognitive theory can be used as a unifying conceptual framework to integrate study of these variables and to discern how they may function together. For example, within the context of this theory, control beliefs are exemplified by the construct of self-efficacy. Self-efficacy, referring to personal beliefs about one's capability to perform particular behaviors or courses of action, has been posited to play important roles in the affective self-regulation process. Relevant research on self-efficacy supports the conclusion that "feeling competent and confident with respect to valued life goals is associated with enhanced well-being."[7(p.156)] Self-efficacy at managing post-cancer challenges has been linked to emotional well-being in cancer survivors.[29] In Bandura's[31] theory, outcome expectations are beliefs about the positive and negative outcomes that are contingent upon one's actions (e.g., "if I do *x*, then *y* will happen"). Perception of positive outcome expectations has been found to relate to satisfaction within particular life domains.[32]

A good deal of research has examined the relation of goals to well-being, and many aspects of goals (e.g., simply having goals, goal importance, goal commitment, goal progress) have been studied. Findings indicate that the perception that one is making progress at meeting personal goals tends to be a very good predictor of well-being.[7] However, the type of goal, and one's reasons for pursuing it, may affect the impact that a given goal has on well-being. Positive effects of goals on SWB appear to be maximized, for instance, when people pursue goals that are personally important to them,[33] congruent with their personal values,[34,35] self-determined and pursued for intrinsic reasons,[36] focused on challenging yet realistic activities,[37] and directed at approach rather than avoidance behaviors.[38]

4.2. Behavioral and Social Variables

A variety of behavioral variables have also been linked to SWB. For instance, Cantor and Sanderson[39] cite the importance of behavioral involvement in personally valued activities. This involvement enables progress on personal goals, brings people into contact with others for mutual social gain, helps them to avoid rumination, provides mastery opportunities, and confers eudaimonic benefits (e.g., sense of purpose, personal identity). Participation in valued life tasks may be particularly beneficial at life transition points where role positions are in flux and questions about life purpose and meaning are salient[40]—which may well be relevant issues for the many cancer survivors who experience disruptions in their work, family, or social lives (Wolff, this volume). A variety of other behavioral (or cognitive–behavioral) variables and strategies have also been found relevant to SWB or psychological adjustment, such as problem-solving, coping methods (e.g., active, problem-focused strategies), and relationship-enhancing skills.[41–44]

Finally, research and theory also point to the important role of environmental supports, particularly social and relational resources, in maintaining and enhancing well-being.[7] Social variables have taken many forms in the well-being literature, for instance, positive relations with others,[45] social connectedness,[46] and attachment.[7] Social support has, in particular, been considered a key facilitator of well-being outcomes, promoting SWB under normative life conditions[33] and alleviating negative affect associated with adverse life events.[40] Social support provides a variety of specific benefits, such as material help, emotional support, companionship,[47] and even positive physical outcomes (e.g., enhanced biological response to stress and neurotransmitter regulation[48]).

5.0. INTEGRATING TRAIT AND SOCIAL–COGNITIVE PERSPECTIVES ON WELL-BEING

Having identified a variety of variables—trait, cognitive, behavioral, and social—that have each been linked to SWB, it is important to consider whether they may be brought together under the umbrella of a common conceptual framework. Such a framework might offer several benefits. For instance, rather than viewing them as entirely orthogonal sources of SWB, an integrative framework may suggest processes by which these variables function together to promote and restore well-being. It might also point to useful strategies for primary and secondary prevention efforts. This section describes one such framework, consisting of two interrelated models. One model emphasizes processes that promote well-being under normative life conditions; the other highlights coping mechanisms used to restore well-being when it has been disrupted by adverse life events.[4] Given the focus of this book on the cancer survival process, more consideration will be devoted to the restorative than to the normative SWB model.

5.1. Maintenance of Normative Well-Being

The model of normative well-being, shown in Figure 1, is designed to integrate a variety of empirical linkages and compatible theoretical positions in the well-being

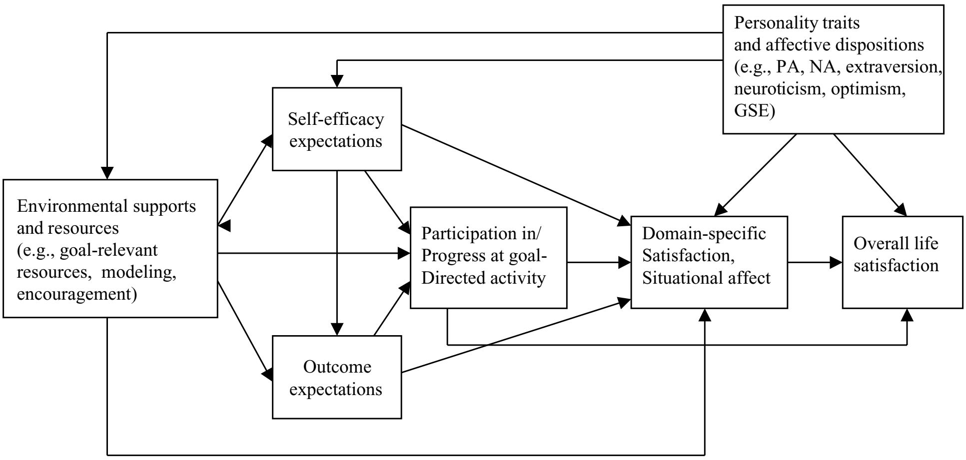

Figure 1. Contributions of Personality, Affective, and Social–Cognitive Variables to Well-Being under Normative Life Conditions. NA = Negative Affectivity; PA = Positive Affectivity; GSE = Generalized Self-Efficacy. Reprinted with Permission from Lent.[4]

literature.[4] The first thing to note is that the model disaggregates the major components of SWB—life satisfaction, positive affect, and negative affect—into separate variables and considers the interplay among them. In particular, the model identifies overall life satisfaction as the key criterion of well-being from a clinical perspective, and posits that life satisfaction is influenced directly by (a) core personality/affective traits, (b) domain satisfaction (i.e., how satisfied individuals feel within their central life domains, such as work and family), and (c) involvement in valued life tasks and, especially, progress at central personal goals.

In a nutshell, life satisfaction is predicted to be greatest when people possess favorable traits (e.g., tendency to experience high positive affect and low negative affect), are satisfied within their most prized life domains, participate actively in tasks they value, and perceive that they are making progress at goals that are most important to them. In addition to these direct influences, life satisfaction is assumed to be influenced indirectly by self-efficacy, outcome expectations, and goal-relevant environmental resources within people's central life domains. For instance, to the extent that people (a) feel efficacious at performing the tasks necessary to achieve their goals, (b) are optimistic that their goal pursuit will lead to valued outcomes, and (c) feel that they have access to resources needed to achieve their goals, they are likely to make progress at their goals and, in turn, to be satisfied in their central life domains. Domain satisfaction then promotes overall life satisfaction. In other words, the effects of self-efficacy, outcome expectations, and environmental resources on life satisfaction are likely to be channeled through domain satisfaction.

Another thing to note about the model is that personality traits are assumed to affect life satisfaction not only directly but also through indirect routes, such as cognitive appraisals of the self and one's life conditions (e.g., those with chronically high negative affect may tend to report lower self-efficacy and to perceive less support for their goal pursuit). In addition, the relation between overall life and domain satisfaction is seen as bidirectional in that people are likely to be happy overall when they are happy in the life domains they care most about and, conversely, general life happiness is likely to spill over into people's various life domains. For instance, a person who prizes his or her work life above all else will tend to be most satisfied with life in general to the extent that he or she is satisfied at work; at the same time, generally happy people are likely to be happy at work (and everywhere else).

This is a general sketch of the normative well-being model, side-stepping for the present purposes details about certain variables, conditions that may moderate relations among particular sets of variables, additional paths of interest, and possible clinical implications. The take-home message for now is that, in the normal course of events, people's sense of well-being (defined in terms of overall life satisfaction and satisfaction within one's most valued specific life domains) is viewed as only partly a matter of personality and affective traits. Traits may well influence satisfaction outcomes both directly and through their linkages to cognitive, behavioral, and social determinants. But people are not just passive bystanders to the "great genetic lottery that occurs at conception."[19] From the perspective of the normative well-being model, people possess the potential to influence their own affective states (i.e., to assert agency), in part through the goals they develop and pursue, the supports they are able to marshal in support of their goals, and the activities in which they choose to immerse themselves. This take-home message contains more than a note of hope for those not blessed with a sunny disposition at birth.

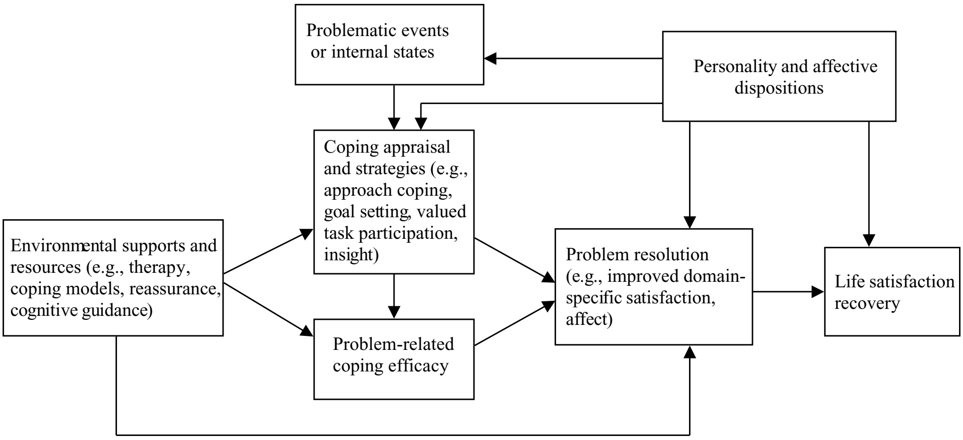

Figure 2. A Model of Restorative Well-Being, Showing the Interrelations of Personality, Affective, and Social–Cognitive Variables in the Coping Process. Reprinted with Permission from Lent.[4]

5.2. Restoration of Well-Being Under Stressful Conditions

While Figure 1 portrays well-being in the normal course of day-to-day functioning, Figure 2 tries to capture the means by which people recover their sense of well-being after it has been disrupted by stressful or traumatic life events. This model is actually an expansion of the first one. That is, normative well-being maintenance processes do not cease functioning during life crises, only to be replaced by separate restorative ones. Rather, in such cases effortful coping mechanisms are assumed to augment the usual things people do to maintain their sense of well-being. As in the first model, personality and affective traits play central roles vis-à-vis domain and life satisfaction, but they do not act alone in steering the affective ship, so to speak—nor does that ship merely function on automatic pilot.

According to the restorative model, the usual SWB maintenance process may become destabilized when people perceive they are faced with problematic external events (e.g., health threats) or internal states (e.g., existential questions) (see the top, central portion of Figure 2). Consistent with Lazarus and Folkman's[49] stress coping model, under such conditions, people engage in a cognitive process of appraising the nature of the stressor (e.g., threat, actual harm or loss, challenge) and whether they have the capabilities or resources to cope with it. Stressors that are deemed especially significant (e.g., life altering), and for which the person believes he/she lacks the necessary coping options, are likely to have the greatest adverse impact on domain and life satisfaction (and, concurrently, depression and anxiety).

Parenthetically, the impact on domain satisfaction is based on the assumption that most adverse events differentially affect particular life domains. For instance, negative work events may diminish job satisfaction and, in turn, overall life satisfaction (to the extent that work is a central life domain for the individual). However, certain events hold the potential to exert a crossover effect on multiple life domains. For instance, job dissatisfaction or loss may adversely affect family relations and, in turn, family satisfaction. More to the present point, facing (and surviving) cancer may affect functioning in and satisfaction across multiple life domains (e.g., work, family, social, and other roles may all become disrupted to varying degrees). The impact on overall life satisfaction, and the coping burden, may be especially pronounced to the degree that a stressor adversely affects satisfaction within multiple life domains.

Getting back to the path model in Figure 2, it may be seen that, where coping efforts are perceived as necessary, people may draw on a variety of strategies. Again, in keeping with stress coping theory, such methods comprise two general categories: problem-focused coping (trying to solve the problem at hand directly) and emotion-focused coping (dealing with the emotional consequences of the problem, such as anxiety).[49] Other schemes for classifying coping methods have also been offered, such as approach versus avoidance coping. The general conclusion is that active efforts at problem-solving are preferable when the stressor is controllable, and emotion-focused efforts (e.g., reframing or accepting the problem) represent a viable approach when the stressor is not controllable.

Problem-related coping efficacy is seen as an important part of the coping process (see Figure 2), partly mediating the effect of coping strategies. Coping efficacy, a form of self-efficacy, refers to people's beliefs in their ability to negotiate particular stressors or obstacles. These beliefs affect whether people construe particular life events as benign, upsetting, or challenging; the actions they take to manage environmental obstacles; and how they deploy their coping strategies.[31,50] Favorable beliefs regarding coping efficacy are likely to help people make the most of the coping methods at their disposal, draw effectively upon environmental supports, and persist at problem-solving efforts when faced with arduous conditions.

Environmental supports and resources comprise a crucial part of the restorative model. People do not cope in a vacuum; they are aided (and sometimes stymied) by the nature of their support systems. Supports and resources include environmental assets like access to coping models, general social support (including such functions as reassurance and cognitive guidance), opportunities to acquire new coping strategies, and interpersonal messages that bolster coping efficacy (e.g., credible exhortations from important others that one has the ability to cope with the stressor; see Lent and Lopez's[51] model of relational efficacy).

As shown in Figure 2, environmental agents may have a direct effect on problem resolution (e.g., by playing an advocacy role), in addition to their indirect effects as sources of coping methods and supporters of coping efficacy. Where natural support systems are deficient or become exhausted, which is sometimes the case in dealing with chronic stressors, professional interventions may be employed to foster new coping methods and to convey support for the individual's coping efficacy. Rather than being methods of last resort, such interventions may well serve the goals of secondary prevention—about which more will be said in a later section.

Finally, let us return to the role of personality and affective traits. As in the maintenance of normative well-being, affective dispositions have key (and multiple) roles to play vis-à-vis the emotional recovery process subsequent to life traumas. As depicted in Figure 2, personality variables, such as positive and negative affect, are seen as influencing restoration of domain and overall life satisfaction both directly (via the natural return to affective baseline process[15]) and indirectly through cognitive and behavioral routes. More specifically, particular traits may affect how people label life events, perceive their coping efficacy, and select coping options. For instance, those with a tendency toward high negative affect may be inclined to respond adversely to problematic life events and to hold less favorable views of their coping abilities. Those with high levels of positive affect or dispositional optimism may, to the contrary, read their circumstances and coping abilities in more favorable terms. More highly extraverted persons may be more inclined to marshal social forms of support (or to have more sources of social support available) than do those high in introversion. Those higher in the trait of conscientiousness may have the advantage of setting and marking progress at their personal goals, which can help to promote and reinstate domain satisfaction. These are just some of the more specific trait-emotional recovery paths that seem plausible.

6.0. FUTURE RESEARCH AND THEORETICAL DIRECTIONS

While many of the individual paths in both the normative and restorative models have been examined in prior research, there is much room for additional inquiry testing the models' predictions. A few particular research needs will be highlighted here.

First, although the models were designed to be consistent with existing research findings, there have been relatively few tests of the full normative model, and no tests of the complete restorative model. Therefore, it would be valuable to test the full set of relations posited by each model or at least major subsets of each model, such as the role of coping efficacy as a mediator of the effects of coping methods and support systems on posttrauma SWB recovery. Second, existing tests of the normative model have mostly involved college students and cross-sectional research designs.[32] What would be particularly valuable at this stage—and, indeed, essential to support extensions of the theoretical framework to practice—would be research involving clinical populations (particularly cancer survivors) and designs capable of testing the tenability of cause–effect relations among the theoretical variables (e.g., longitudinal research). Such research might especially focus on the posited pathways through which traits affect domain and life satisfaction, and the unique contribution that cognitive, behavioral, and social variables are assumed to make, above and beyond the effects of traits.

Third, there is need to design interventions derived from the theory, testing their efficacy against relevant comparison conditions (e.g., no-treatment control, patient education, standard cognitive–behavioral therapy). Intervention research could provide convincing tests of causality (e.g., does goal-directed activity enhance, rather than merely predict, improved domain-satisfaction?). It would be valuable for such research to focus on cancer survivors and those coping with other stressful life conditions, and to examine the potential impact of psychosocial interventions on physical outcomes.[48] Theory-derived interventions could take various forms, ranging from remedial verbal therapy to more proactive efforts at secondary prevention (e.g., community workshops, structured groups). The latter may be particularly worth pursuing, given their potential to forestall more serious emotional difficulties and to potentiate patients' naturally occurring strengths and support systems.

Finally, it is worth emphasizing that emotional well-being, no matter how important in and of itself, represents only one aspect of psychosocial adjustment. Other important dimensions would include, for example, the absence (or tolerable levels) of psychological symptoms and the adequacy of role functioning in one's major life spheres.[4] Comprehensive study of the posttrauma recovery process, including tests of the restorative well-being model, would therefore do well to include multiple indicators of psychosocial adjustment that are assessed from multiple perspectives (e.g., self, significant others, work associates).

7.0. CLINICAL IMPLICATIONS OF THE RESTORATIVE WELL-BEING MODEL

Although the restorative (and normative) models may hold useful implications for assisting cancer survivors to recover their emotional equilibrium, it should be noted that the suggestions offered in this section are largely speculative. They are a sampling of intervention possibilities that can be derived from the theory and relevant research in the well-being literature. Research is needed to assess the extent to which the theory can be generalized specifically to the experiences of cancer survivors. The theory was included in this Handbook in an effort to promote a more comprehensive framework for understanding the process of emotional recovery in cancer survivors. It is hoped that this conceptualization will assist researchers and clinicians to integrate findings and generate new approaches to aid survivors in their efforts to regain and maintain a sense of well-being.

7.1. Cognitive, Behavioral, and Social Routes

Pending further research, I believe that the model points to several potentially valuable cognitive, behavioral, and social targets and resources for assisting cancer survivors to contribute to their own affective regulation. None of these should be seen as a "silver bullet." Rather they compose a sort of "ordinary magic" that allows people to display emotional resilience in ways that may seem mundane but, nevertheless, can make a large difference to those facing adverse conditions. They also resemble personal and environmental resources and strategies that have been identified in the developmental resilience literature.[52]

One potential target lies in the goal-setting process. The cancer experience may, among other things, have disrupted some patients' (a) access to, or enjoyment of, their central life domains (e.g., work may have been temporarily halted or a valued job may have been lost) and/or (b) progress toward valued life goals. Thus, a useful clinical focus may be to identify current life goals as well as those that have been blocked or impeded by the cancer experience. Steps can be taken to explore the possibility of reviving or transforming former goals, avenues for setting new goals, resources needed for goal pursuit, methods to mark progress at goal pursuit, and ways to celebrate success and respond to disappointment. By making explicit a process that is often implicit in most people's lives, cancer survivors may see new opportunities for influencing their own domain and life satisfaction.

A second target, and one quite consistent with goal-setting, may entail a focus on getting survivors reengaged with valued life activities that may have been foreclosed or limited by the cancer experience. As noted earlier, such activities lend a sense of structure and purpose to life, provide a context for goal pursuit and value fulfillment, and can help ward off rumination and social isolation. Choice of activities is an individual matter but, in general, activities that have an outward focus and involve social interaction may be particularly useful.[39,53] Among other things, social activities (e.g., interactions with friends, community service) contain opportunities for both receiving and giving social support. Activities that have the potential to promote "flow," whether they are social or not, may also be intensely enjoyable. (Flow is a state of complete absorption that is associated with involvement in skill-stretching activities[37]).

The importance of reentry, or increasing involvement, in valued life activities can probably not be overemphasized. At least some of the emotional impact of the cancer experience—apart from its existential threats, pain, and discomfort—may be due to its potential to obstruct access to the pleasurable activities in which patients would normally immerse themselves.[54] To the extent that patients develop depressive symptoms, they may further avoid social and other formerly pleasure-inducing situations, perpetuating a negative emotional spiral. Viable routes to curtail that spiral might include aiding patients to (a) identify and reengage in activities that formerly brought them enjoyment, (b) explore new options for such involvement, and (c) remain as actively engaged as possible in their usual valued life tasks during the course of cancer treatment. The latter option has the obvious advantage of minimizing disruptions in valued life domains from the beginning, thereby lessening any negative effects on SWB. Of course, such activity-promoting efforts need to take into account such considerations as the patient's physical stamina and the possible side effects of his/her treatment regimen. Cognitive techniques may be useful to help the patient accept his/her current limitations, set reasonable performance standards, and focus on incremental steps toward desired levels of activity involvement or skill proficiency.

Many other potential coping strategies can be gleaned from the literatures on well-being, psychological resilience, and posttraumatic growth. For instance, emotional and other benefits may be obtained through physical exercise,[53] relaxation,[55] social support seeking,[48] and therapeutic writing.[56] The latter activity may offer the opportunity to gain insight and perspective on the cancer experience, including identifying potential positive aspects of the experience (e.g., valuable lessons learned about oneself, reprioritization of one's values and goals, strengthening of relational bonds). Many survivors spontaneously discover such benefits; indeed, 47% of the respondents in Wolff's (this volume) survey indicated that dealing with cancer had positive effects on their lives. Although therapeutic writing can provide a helpful structure for persons to find their own meaning in stressful life events, deliberate efforts to promote "benefit-finding" need to be approached with caution because some may experience them as insensitive to the burdens they have had to endure.[57]

7.2. Secondary Prevention and Remedial Efforts

Many of the cognitive and behavioral strategies mentioned above may develop naturally as a consequence of survivors' interactions with their support systems. However, not all persons are fortunate enough to have adequate support systems, and even some that do may not be ideally positioned to plumb their support systems for the things they need to foster their own emotional recovery. In such situations, secondary prevention efforts may provide an excellent opportunity to empower survivors' own natural tendencies toward emotional recovery, while monitoring their progress at containing psychological symptoms such as anxiety and depression.

When structured as group interventions or workshops, secondary prevention may have the added benefits of efficiency and can capitalize on curative conditions that are unique to group settings (e.g., sense of universality). Moreover, composing groups that contain members or facilitators who have been living with cancer for differing lengths of time can allow more experienced cancer survivors to serve as potent coping models, promoting the coping efficacy and strategies of those newer to the cancer experience. It is noteworthy that 70% of the participants in Wolff's survey (this volume) indicated that they would assist in survivorship activities. The involvement of more experienced cancer survivors may well benefit themselves[27] as well as others, for example, by contributing to one's sense of life purpose and "mattering."

Surprisingly, relatively few of Wolff's respondents reported that they had participated in either counseling or support groups—even though sizeable percentages of them had experienced considerable problems in coping and many were dissatisfied with aspects of their natural support systems. The reasons for this disparity between need and help-seeking are unclear and probably complex. However, to the extent that part of the problem involves lack of (or difficulty accessing) services, innovative technological options might be considered. For example, the Internet has been used recently as the medium for delivering a well-being intervention to large numbers of participants,[26] and online cancer support resources have been available for some time.[58] There is much room for the design and testing of additional innovative, theory-based virtual support groups, workshops, or well-being exercises for cancer survivors.

In certain cases, more remedial, psychotherapeutic interventions may be helpful for survivors who are having an especially difficult time regaining a sense of emotional well-being. Some of these may include persons with a preexisting tendency toward high negative affect. For them, the cancer experience may have exacerbated a natural susceptibility to negative emotions and a penchant for interpreting life experiences in pessimistic terms. Brown *et al.*[22] offer useful suggestions for working with clients prone to experience high negative affect. Their perspective suggests that it may be more fruitful to deal with the cognitive and behavioral concomitants of this predisposition (e.g., helping clients to recognize, accept, and learn to work with their negative moods) than to try to change their personalities.

Where more intensive intervention seems indicated, it may be useful to employ cognitive behavioral therapy (CBT) techniques. CBT has been shown to produce substantial short-term effects on depression, anxiety, and QOL indicators—and continuing, if more modest, effects on QOL in cancer survivors at follow-up assessments (8 months or more postintervention).[3] (It will be recalled that QOL indicators often include measures of life satisfaction.) These effects were more marked in individual than in group interventions. By contrast, patient education interventions had little effect on symptoms or QOL.

CBT is entirely consistent with the sort of treatment elements that might be derived from the restorative model. In addition to the typical treatment elements in CBT interventions, the restorative model would imply a particular focus, as suggested above, on expansion of coping and problem-solving strategies, bolstering of coping efficacy, assistance in building and/or accessing natural social supports, identification of options for valued life participation and goal pursuit, and special attention to negotiating issues that might impede task involvement and goal progress (e.g., environmental barriers, downward cognitive comparisons between one's former and current capabilities, unreasonable performance standards that focus only on ultimate goal attainment rather than incremental progress toward one's goals). In fact, given the well-documented ability of goal progress to promote well-being in nonclinical settings,[7] a good portion of therapy might fruitfully revolve around the goal setting and pursuit process, thereby empowering clients to exert a greater measure of affective self-control.

Augmenting this admittedly problem-focused coping orientation, interventions might well include an emotion-focused agenda (e.g., achieving insight, reframing negative events as challenges and opportunities for growth). Indeed, various emotion-focused coping strategies (e.g., emotional expression[59]; acceptance, use of humor[42]) have been found to be helpful in breast cancer patients. Emotion-focused counseling might profitably deal as well with the continuing worries about death and the recurrence of cancer that many survivors experience (Wolff, this volume). This balance of problem-focused and emotion-focused strategies recalls the "serenity prayer" in its implicit acknowledgment of those things over which one has some control (e.g., involvement in valued activities, choice of goals) as well as those that cannot be controlled (e.g., whether the cancer will ultimately return, how long one will live).

In sum, the overarching goal of secondary prevention or remedial intervention derived from the restorative model is to promote enhanced domain and life enjoyment, ideally through agentic and nonchemical means. Such an approach may call for a day-at-a-time philosophy (e.g., "what can I do today that would give me pleasure or help me progress toward my goals?") since goal-directed activity is an ongoing process rather than an ultimate destination. While psychosocial interventions may not optimally affect physical functioning or survival rates in the aftermath of cancer,[3,60] they may nevertheless hold great potential to promote recovery of emotional well-being and other aspects of adjustment, thereby enabling cancer survivors to derive as much pleasure and productivity from life as their temperaments and the vagaries of human mortality will allow.

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Chapter 14

Physical Activity for Cancer Survivors

Potential Benefits and Guidelines

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1.0. INTRODUCTION

Interest in the potential of exercise as a therapeutic intervention for a wide range of clinical populations is growing steadily. A body of research has established physical activity as having a role in the prevention and/or management of several chronic medical conditions,[1] including coronary heart disease,[2] stroke,[3] hypertension,[4] non-insulin-dependent diabetes,[5] obesity,[6] musculoskeletal disorders,[7] and mental health problems.[8]

Evidence of the effects of physical exercise in protecting against cancer has been emerging since the 1960s. More recently research attention has turned to the potential benefits of exercise for individuals already diagnosed with cancer. This chapter summarizes the evidence available so far in this area, and outlines the new directions being taken to advance understanding of the value of physical activity across the cancer spectrum: from prevention, through detection, treatment, and palliation, toward long-term survivorship.

2.0. HEALTH CHALLENGES FOR CANCER SURVIVORS

The challenges to health and well-being faced by cancer survivors can be quite diverse depending on the site and stage of cancer, as well as characteristics such as age and gender. In addition to the effects of the disease, receiving a diagnosis of cancer and undergoing cancer therapy can result in a range of negative side effects that diminish quality of life. Common physical consequences of surgery and adjuvant therapy include impaired cardiopulmonary function, deterioration in lean body tissue and muscular strength, and decreased range of motion.[9] These can all impact on the ability to carry out activities of daily living (e.g., dressing, housework, childcare, shopping, gardening), occupational work, and social activities, and can be further compounded by fatigue. Cancer-related fatigue is characterized by complete lack of energy and severe mental exhaustion, and is one of the most common and most distressing symptoms reported.[10]

Alterations in body weight and body composition affect many cancer survivors. Weight loss is a typical symptom of many cancers, and both chemotherapy and radiotherapy can cause mucositis, anorexia, and nausea, making food intake difficult.[11] Conversely, weight gain is associated with some chemotherapy protocols used in treating breast cancer,[12] and increased appetite caused by some steroid treatments. Reduced activity during and after cancer treatment also contributes to weight gain. Further side effects include pain, sleep disturbances, cognitive impairments (e.g., forgetfulness, inability to concentrate),[13] and a host of psychological sequelae.[14] These can range from clinical depressive or anxiety disorders, to occasional feelings of anger, guilt, confusion or loneliness. Loss of self-esteem, and concerns over body image, are also frequently reported. Psychological distress may persist long beyond the end of treatment in some cancer survivors,[15,16] and can have a significant impact on the ability of some individuals to return to work.[17]

3.0. HEALTH-RELATED EFFECTS OF EXERCISE

Exercise has a range of physiological effects, many of which are potentially beneficial for cancer survivors at the time of treatment and afterwards. Some of the likely benefits of regular physical activity for cancer survivors are related to improvements in health-related fitness components. These are particularly relevant to the ability of individuals to carry out activities of daily living, and are associated with a lower risk of diseases linked to a sedentary lifestyle.[18] The components of health-related fitness are cardiorespiratory fitness, muscular fitness, body composition, and flexibility.[18]

Cardiorespiratory fitness refers to the ability to maintain a level of physical activity for a continuous period of time and involves the cardiovascular, respiratory, and musculoskeletal systems of the body.[18] Cardiorespiratory fitness has been shown to be a strong predictor of mortality in both healthy individuals and those with a chronic illness.[19] This type of fitness is developed through aerobic exercise, consisting of repetitive, continuous movement of the body's large muscle groups (e.g., walking, jogging, cycling, swimming).[20] Aerobic exercise training is associated with improvements in a wide range of outcomes: cardiovascular and respiratory function, exercise capacity and endurance, resting heart rate, blood pressure, glucose tolerance and lipid profile, body composition, functional abilities and work, recreational, and sport performance, psychological well-being, depression, and anxiety. Through these effects, cardiorespiratory fitness is effective in preventing, and/or managing, a number of chronic illnesses.[18,21,22]

Muscular fitness can be subdivided into strength and endurance components. Muscular strength is the ability of a specific muscle (or group of muscles) to generate force (also referred to as maximum voluntary contraction or MVC), while muscular endurance is the ability of the muscle to complete a repeated number of contractions over time.[18] Recent evidence suggests that muscular fitness, independent of aerobic exercise, is associated with mortality.[23] Resistance training is the primary mode of improving both muscular strength and endurance. Benefits of resistance training include improvements in: bone mass/density, glucose tolerance, resting metabolic rate, fat-free mass, exercise capacity, postural stability and balance, and performance of activities of daily living.[18]

Body composition refers to the relative percentages of fat mass and fat-free mass that make up the body.[18] Specific measurements of body composition provide better estimates of body fat than do those based simply on weight, height, and/or circumferences.[18] Individuals with large amounts of body fat are at greater risk of developing various chronic illnesses.[6] Improvements in body composition can be achieved through both aerobic exercise and resistance training, and may act through increases in total caloric expenditure, fat-free (lean) body mass, and resting metabolic rate.[6] These favorable changes to body composition can result in decreased risk of numerous medical conditions including some cancers.[6]

Flexibility is defined as the ability of a joint (or joints) to move through a complete range of motion (ROM) and plays an important role in the ability to perform activities of daily living.[18] The performance of regular stretching exercises specific to each joint is required to maintain or improve flexibility.[18] This may improve joint ROM and function, and enhance muscular performance resulting in improved functional abilities.[20] Furthermore, regular flexibility training may play a role in reducing the incidence of, and treating, musculoskeletal injuries.[20]

4.0. EVIDENCE FOR PREVENTION AND SURVIVAL OUTCOMES

The evidence that physical activity can prevent cancer has been accumulating since a seminal study of railway workers in 1962 that demonstrated a 30% reduced risk in cancer mortality among section men compared with clerks.[24] There are currently more than 180 epidemiological studies investigating the association between physical activity and cancer risk. Evidence for risk reduction attributable to physical activity is considered “convincing” for colon and female breast cancer, “probable” for endometrial cancer, and “possible” for prostate and lung cancer. Lower risk at other cancer sites (i.e., testicular, ovarian, kidney, pancreas) has also been reported, but the evidence is “insufficient” at this time due to the small number of studies.[25,26]

The biological mechanisms behind the apparent protective effects of physical activity have not been established, but several systemic and site-specific mechanisms have been suggested.[25] Systemic effects of physical activity include the modification of metabolic hormones and growth factors, improvements to the antitumor immune defence system, and regulation of energy balance and fat distribution. Physical activity may also promote antioxidant defence and DNA repair. Additional site-specific mechanisms include alterations in levels of sex steroid hormones (e.g., estrogens, progesterone, and androgens) that are implicated in hormone-dependent cancers such as breast, endometrial, ovarian, and prostate. In the case of colon cancer, decreased gastrointestinal transit time may reduce exposure to carcinogenic agents, and changes to levels of insulin, prostaglandin, and bile acids may inhibit colonic cell proliferation. Improved pulmonary ventilation and perfusion may help to prevent lung cancer through minimizing the presence of carcinogens in the airways.

Although there are currently insufficient empirical data to establish the precise mechanisms for the anticarcinogenic effects of physical activity,[27] it is an area of considerable research activity. Furthermore, it is feasible that some of the mechanisms thought to be responsible for the role of exercise in the primary prevention of some cancers, may also confer benefits in terms of secondary prevention outcomes such as disease recurrence and survival.

4.1. Cancer Mortality and Recurrence

There is limited research on the effect of physical activity on disease recurrence and mortality in cancer survivors, with data available from four studies so far. In a randomized trial of group psychotherapy in 66 metastatic breast cancer survivors, self-reported regular exercise was the only nonmedical variable to predict survival.[28] In a recent cohort study, the amount of self-reported leisure-time physical activity was assessed in 41,528 Australians, among whom 526 cases of colorectal cancer were identified.[29] Those who reported regular exercise (at least once a week) prior to diagnosis, had improved cancer-specific survival (73% 5-year survival) compared with those not reporting regular exercise (61% 5-year survival). In addition, cancer-specific mortality was higher in those with higher body weight, percent body fat, and waist circumference: all factors that can be positively influenced by physical activity. The observed association between exercise and cancer-specific mortality was also influenced by cancer stage and site. A greater risk reduction was observed for those with stage II and III compared with stage I and IV cancers, and in those whose cancer originated in the right colon, rather than the left colon or rectum. Recurrence was not assessed in this study. Another study involving 816 patients with stage III colon cancer, observed increases in recurrence-free survival, disease-free survival, and overall survival in association with increasing volumes of physical activity.[30] After controlling for various demographic and medical variables, those performing at least 18 MET-hours of exercise per week (equivalent to 1 hour of brisk walking 6 days per week) had a 49% reduction in risk of recurrence or death compared with those performing <3 MET-hours per week over a 3-year period following surgery and chemotherapy.

Using data from the Nurses Health Study, the amount of self-reported leisure-time physical activity was assessed in 2987 female breast cancer survivors after diagnosis.[31] Women who reported at least 3 MET-hours of physical activity (equivalent to 1 hour of walking) per week or more, had a decreased risk of recurrence or cancer-specific mortality compared with women who reported less physical activity. A further reduction in risk of recurrence and cancer-specific mortality was seen with higher levels of physical activity, up to 23.9 MET-hours per week. Overall, 5-year survival was 93% for <3 MET-hours per week, 97% for 3–8.9 MET-hours per week, and 97% for ≥9 MET-hours per week. The corresponding rates for 10-year survival were 86%, 89%, and 92%. In addition, this risk reduction held for normal weight (BMI <25), overweight (BMI 25–30), and obese (BMI >30) women who engaged in 9 or more MET-hours per week. However, the benefits of physical activity (<9 versus >9 MET-hours per week) appeared to be limited to women with hormone-responsive tumors. This finding was based on small numbers of deaths so further research is required to determine the impact of tumor characteristics on the relationship between physical activity and cancer recurrence and cancer-specific mortality. Further data on the effects of exercise on cancer recurrence is currently being collected from a cohort of over 1200 breast cancer survivors and 1000 prostate cancer survivors who participated in case-control studies.[32,33]

4.2. Cancer Biomarkers

Studies assessing recurrence and mortality obviously take many years to perform. Other studies are focused on the shorter-term effects of physical activity on intermediate biological markers that are thought to lie on the causal pathway between exercise and cancer recurrence or mortality. These trials provide important data on the potential mechanisms by which exercise may influence disease progression and survival.

4.2.1. Sex Steroid Hormones

Cumulative lifetime exposure to sex steroids, particularly estrogens has been linked to breast, endometrial, and ovarian cancer, while androgen exposure has been linked to prostate cancer. Physical activity has been shown to lower estrogen levels in premenopausal women through a continuum of alterations in menstrual cycle function.[34] Furthermore, for postmenopausal women, exercise leads to reductions in body fat, and increases in sex hormone binding globulin concentration, resulting in less bio-available estrogens and androgens in both men and women.[25]

The effects of a 12-month aerobic exercise intervention were examined in 173 sedentary, overweight, postmenopausal women without cancer.[35] The exercise group had a significant decrease in estrone, estradiol, and free estradiol compared to no change or increase in the control group at 3 months. These differences were maintained at 12 months, but were no longer statistically significant. A similar nonsignificant decrease in androgens was noted in both groups. However, those who lost weight had a significant decrease in testosterone and free testosterone, which was greater in the exercise group than the control group despite similar weight loss. To date, the effect of physical activity on sex steroid hormones in cancer survivors has only been examined in a small pilot study of nine breast cancer survivors who engaged in an 8-week physical activity (3 times per week of aerobic activity) and low fat diet (20% calories from fat) intervention.[36] Slight, nonsignificant decreases were observed in serum concentration of total and free estradiol, estrone sulfate, total testosterone, androstenedione, and dehydroepiandrosterone.

4.2.2. Body Composition

Higher body weight is associated with increased risk of colon, kidney, esophageal, endometrial, thyroid, and postmenopausal breast cancer.[37] In addition, abdominal fat is proposed to result in higher cancer risk than overall body fat.[38] Physical activity and reduced dietary intake can decrease body weight, while physical activity may preferentially reduce intra-abdominal fat[38] and is associated with improved weight maintenance after weight loss.[25]

In randomized controlled trials of physical activity in breast cancer survivors, a 12-month resistance intervention in 85 women resulted in a significant increase in lean body mass and significant decrease in percent body fat, with no change in overall body weight, BMI, or waist circumference,[39] while a 15-week aerobic activity intervention in 52 women did not result in a change in body weight, BMI, or sum of skinfolds.[40] In a trial of a 3-month aerobic intervention in 123 women, no overall change in body weight between the supervised exercise group, home-base exercise group, and control group was recorded.[41] However, when type of cancer treatment was considered, in those not receiving chemotherapy, the supervised exercise group lost body weight while there was a slight increase in both the home-based and control groups. In a randomized controlled trial of physical activity in 155 prostate cancer survivors undergoing androgen deprivation therapy, no change in body weight, BMI, waist circumference or sum of skin folds was noted.[42]

4.2.3. Metabolic Hormones

Higher insulin and IGF-1 levels have been associated with increased cancer risk.[25] Physical activity decreases insulin and increases IGFBP-3, which binds IGF-1 limiting its bioavailability, while the evidence for changes in IGF-1 is mixed.[25]

In 443 colorectal cancer survivors who reported leisure time physical activity prior to diagnosis, no difference in IGF-1 or IGFBP-3 was observed by activity level and no association with cancer-specific mortality existed.[43] However, in the physically active group, those in the highest quartile of IGFBP-3 had a significant decrease in cancer-specific and all-cause mortality. No association was demonstrated for the inactive group. In the randomized controlled trials with breast cancer survivors described above, the 12-month resistance program resulted in a significant decrease in IGF-II but no change in fasting glucose, insulin, insulin resistance, IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3,[39] while the 15-week aerobic exercise program resulted in a decrease in IGF-1 and increase in IGFBP-3, with no change in fasting glucose, insulin, insulin resistance, IGF-II, IGFBP-1, or IGFBP-2.[44]

4.2.4. Immune Function and Inflammatory Markers

An improvement in antitumor immune defences could potentially impact all cancer sites.[25] Physical activity has been shown to increase the number and activity of macrophages, as well as lymphocyte activity and proliferation.[25] Furthermore, physical activity may reduce systemic inflammation[45] which has been linked to numerous chronic health conditions, including cancer.[46]

In the randomized controlled trial in 52 breast cancer survivors previously described, a 15-week aerobic exercise intervention resulted in an increase in natural killer cell cytotoxic activity and unstimulated [H^3]thymidine uptake by peripheral lymphocytes.[44] Furthermore, there was a nonsignificant decrease in high-sensitive c-reactive protein, a marker of inflammation that has been linked to cardiovascular disease.[47] A trial of 35 stomach cancer patients undergoing surgery also reported increased natural killer cell cytotoxic activity.[48] Positive correlations between natural killer cell function and both recurrence and cancer-specific mortality have been suggested.[49]

Overall, there has been limited research on the effects of physical activity on proposed biomarkers of cancer recurrence, cancer-specific mortality, or all-cause mortality. Thus far, compelling evidence for the mechanisms through which physical activity may influence secondary prevention in cancer does not exist. However, research efforts are continuing in the attempt to validate biomarkers and understand the effects of exercise on these intermediate outcomes, with the ultimate aim of increasing disease-free intervals and overall survival.

5.0. EVIDENCE FOR REHABILITATIVE OUTCOMES

Although there is increasing interest in investigating the potential effects of exercise on disease and survival outcomes, the majority of research on exercise for cancer survivors so far has been directed at outcomes relating to treatment management and rehabilitation.

Since the pioneering work of Maryl Winningham of Ohio State University College of Nursing during the 1980s,[50–52] the volume of research in this area has grown exponentially. By the close of the 20th century, more than 60 journal articles

Table 1. Recent Systematic Reviews of Exercise for Cancer Survivors

Authors	Review	Reviewer conclusions
Conn *et al.*[54]	Systematic review of 30 intervention trials with meta-analysis	Exercise interventions resulted in small positive effects on health and well-being outcomes among existing studies.
McNeeley*et al.*[62]	Systematic review of 14 randomized breast cancer trials with meta-analysis	Preliminary evidence suggests that exercise is an effective intervention to improve quality of life, cardiorespiratory fitness, physical functioning, and fatigue.
Schmitz *et al.*[67]	Systematic review of 32 controlled trials with meta-analysis	Physical activity improves cardiorespiratory fitness during and after cancer treatment, symptoms and physiologic effects during treatment, and vigor posttreatment.
Knols *et al.*[61]	Systematic review of 34 controlled trials	Cancer patients may benefit from physical exercise both during and after treatment.
Douglas[57]	Systematic review of 21 intervention studies	There is a growing body of evidence to justify the inclusion of exercise programs in the rehabilitation of cancer patients returning to health after treatment.
Galvão and Newton[59]	Systematic review of 26 intervention studies	Preliminary positive physiological and psychological benefits from exercise when undertaken during or after traditional cancer treatment.
Stevinson *et al.*[70]	Systematic review of 33 controlled trials with meta-analysis	Exercise interventions for cancer patients can lead to moderate increases in physical function and are not associated with increased symptoms of fatigue.
Oldervoll *et al.*[64]	Systematic review of 12 randomized controlled trials	Cancer patients benefit from maintaining physical activity balanced with efficient rest periods.

or theses had been written on exercise after cancer diagnosis, and half a decade later, the body of evidence now comprises well over 200 reports. Furthermore, the geographic spread of research activity has widened considerably over this time and includes studies conducted in at least 15 different countries across six continents.

A number of review articles have been published that attempt to summarize the results and implications of individual studies.[53–72] Conclusions from reviews have been consistently positive with regard to the potential benefits of exercise during cancer therapy and after treatment completion. Table 1 summarizes the conclusions of recent systematic reviews that have evaluated the evidence.

5.1. Physical Function

The most consistent and positive effects demonstrated in randomized clinical trials relate to physical function outcomes. Results of meta-analyses show moderate improvements in cardiorespiratory fitness among cancer survivors engaging in aerobic exercise programs during, and after, cancer treatment.[54,62,67,70] The benefits of preserving fitness during treatment, and gradually increasing it again afterwards, are considerable in terms of being able to perform daily activities and continuing with leisure pursuits.

Similarly encouraging functional outcomes have been demonstrated in trials that have focused on resistance exercise training. Reductions in shoulder pain and disability were reported in head and neck cancer survivors who had undergone spinal accessory neuropraxia/neurectomy,[73] and increases in muscular fitness[42] and muscle mass[74] have been found for prostate cancer survivors receiving androgen deprivation therapy. Increased muscle mass was also demonstrated in breast cancer survivors following a 6-month weight training program.[39] If resistance exercise helps to prevent or reverse the loss of muscle tissue that can result from inactivity, inadequate nutrition, or cachectic processes, it would make a significant contribution to cancer survivors' functional abilities.

5.2. Treatment Side-Effects

There is some preliminary evidence that exercise can help in the management of treatment-related symptoms or side effects.[67] A serendipitous finding of one of the early trials by Winningham and MacVicar was reduced nausea following exercise in breast cancer survivors on chemotherapy.[51] A subsequent trial found that more participants reported reduced nausea in the exercise group, compared with the control participants.[75] Other trials have found fewer sleep problems reported by breast cancer survivors undertaking walking programs during chemotherapy[76] and radiation treatment,[77] than those receiving usual care. Another trial involving inpatients receiving high-dose chemotherapy following peripheral blood stem cell transplantations demonstrated a range of positive outcomes for those exercising daily on a supine cycle ergometer, compared with control participants.[78] These outcomes included lower pain severity and less use of analgesics, lower severity of diarrhea, shorter duration of thrombopenia and neutropenia, and shorter hospitalizations.

Cancer-related fatigue has been identified as one of the most common and distressing symptoms reported by patients, and also one of the most difficult to treat.[10] An overemphasis on rest carries the likelihood of causing increased fatigue, due to individuals becoming caught in a vicious cycle of inactivity that leads to further deconditioning, hence greater fatigue upon even minimal exertion. Some trials have reported reductions in fatigue in participants exercising during treatment,[42,76,77] and those who have completed treatment.[40,79] However, not all trials have demonstrated this effect, and the results of meta-analyses are conflicting on this outcome, with no significant change in fatigue found in three reviews,[54,67,70] but a small significant reduction in another.[62] It is important to note that there is little evidence of increased fatigue from exercise. This is a highly positive finding with respect to the understandable concerns of patients and caregivers that exercise may cause or exacerbate existing fatigue. Instead, current evidence suggests that by adhering to a graded exercise program, cancer survivors can maintain or increase their level of conditioning and function, thereby avoiding becoming trapped in a perpetuating cycle of deteriorating physical function and increasing fatigue.

Exercise has been suggested as useful method of reversing unwanted weight gain in cancer survivors.[80] Although, some studies have reported improved body composition (i.e., increases in lean/fat tissue ratio)[39,74,79,81–83] there is no evidence of significant changes in total body weight.[67,70] It may be that most clinical trials of exercise have been of insufficient duration to affect body weight, and that this outcome is better addressed in longer-term health promotion protocols. A recent systematic review of trials in breast cancer survivors, concluded that the evidence for improved body composition was sketchy, but encouraging.[84]

5.3. Quality of Life

Many trials have measured the effect of exercise interventions on quality of life or psychological well-being in cancer survivors. Some promising results have been reported for breast cancer patients both during and posttreatment for overall quality of life,[40,85] anxiety,[77,86] depression,[41,76,86] body image,[76,77] and self-esteem.[40,87]

Quality of life was also enhanced in two prostate cancer trials.[42,74] However, other trials have been published which found no difference between exercise and control groups in measures of quality of life and psychological distress.[88–90] and the results of meta-analyses have also been conflicting for these outcomes.[62,67]

6.0. RISKS OF EXERCISE

Clearly, for exercise to be considered a valuable intervention that can be routinely recommended to cancer survivors, it must have a positive risk–benefit ratio. The risks associated with exercise at levels required for health promotion, are low in the general population. For cancer survivors, concerns relate to the possibility of exercise leading to immunosuppression, falls, bone fractures, complications of cardiotoxic treatments, exacerbation of pain and other symptoms, and interference with treatment completion or efficacy.

Systematic reviews of trials with cancer survivors have reported few adverse events associated with exercise. However, it should be noted that clinical trials have rigorous screening criteria and exclude participants for whom exercise may pose a potential risk (e.g., those with uncontrolled cardiovascular or pulmonary disease, existing musculoskeletal disorders, or cancer-related conditions such as severe cachexia, anemia, neutropenia, thrombocytopaenia, or metastatic bone disease). Studies that have addressed the role of exercise in causing or worsening lymphedema in breast cancer survivors who have undergone axillary node dissection, have found no increased risk with upper body physical training.[91–93]

In assessing the risk–benefit ratio of exercise, it is important to consider the potential harm to cancer survivors of remaining inactive, alongside the possible hazards of exercise. Physical inactivity leads to deconditioning, bone loss, and muscle atrophy, decreases in glucose metabolism, insulin sensitivity, digestive function and immunosurveillence, and increases in cardiovascular risk factors (e.g., lipid levels, blood pressure). Maintaining regular activity is essential therefore for reducing the risk of developing other chronic conditions (e.g., diabetes, cardiovascular disease, osteoporosis), and particularly so for cancer survivors who may at increased risk of further disease.[94–96]

7.0. SUMMARY OF EVIDENCE

The conclusions of all reviews of the evidence are largely favorable toward exercise as a generally beneficial and safe intervention for cancer survivors. However, all include caveats regarding the inconsistencies among results, and the heterogeneity and methodological rigor of trials. Considerable diversity between trials in the study participants, exercise interventions, and outcomes assessed, make comparisons difficult. Furthermore, methodological limitations were common, particularly in the earlier trials. Common weaknesses are listed in Table 2. Encouragingly, methodological rigor has improved in more recent trials, increasing the validity of the reported findings.[61,70]

The most clearly demonstrated benefit of exercise for cancer survivors is improved physical function, without exacerbation of fatigue or other adverse effects. This strongly implies that patients should attempt to remain active during their treatment, and progressively increase their activity posttreatment to avoid becoming trapped in a perpetuating cycle of deteriorating physical conditioning and increasing

Table 2. Common Methodological Limitations in Clinical Trials of Exercise Interventions for Cancer Survivors

Common methodological limitations of trials	
Sample	• Small and inadequately powered to detect clinically important changes • Convenient rather than representative samples
Group allocation	• Randomization not (or inadequately) used • Inadequate allocation concealment procedures
Assessment	• Primary outcomes not predefined • Multiple outcomes measured and not corrected for in analysis • Lack of blinded assessment
Analysis	• Lack of intention-to-treat analysis • Post-hoc subgroup analysis

fatigue. Preliminary evidence suggests that a range of other positive outcomes are also possible, including lower risk of recurrence, increased survival, and enhanced immune function, quality of life, and psychological well-being.

8.0. EXERCISE PRESCRIPTION GUIDELINES FOR CANCER SURVIVORS

The health-related fitness components of exercise that were discussed earlier, play a key role in the cancer survivor's ability to maintain activities of daily living and other work-related or leisure activities. Therefore, an exercise training program designed to improve each of these components may play a significant role in improving functional capacity in cancer survivors.

As with other clinical populations, cancer survivors should be thoroughly screened prior to commencing any exercise program.[97] The screening process should include a medical examination, consisting of a complete medical history, a physical exam, and laboratory tests as necessary.[18] A form such as the Canadian Society of Exercise Physiology (CSEP)'s PARmed-X is a useful tool that exercise professionals can supply to medical staff to ensure that an individual's ability to undergo a fitness assessment and begin an exercise program, is assessed appropriately.[98] Following medical clearance, assessments to determine the current status of each health-related fitness component should be completed to establish baseline fitness levels. The American College of Sports Medicine (ACSM)[18] provides current guidelines for exercise testing and prescription regarding specific fitness assessment techniques. This information will allow an exercise prescription to be tailored according to the individual's strengths and weaknesses in order to maximize the benefits of the training program. Whether the selected fitness assessments of cardiorespiratory and muscular fitness should be maximal or submaximal in nature will depend on a number of factors including the individual's current health status and medical history, the expertise of the assessor, and the equipment available. However, these assessments should test each person to at least the minimum level anticipated for the training program, to ensure they are physically and medically able to begin the program.[97] Proposed contraindications regarding exercise testing have been described,[99] and should be considered before conducting fitness assessments with cancer survivors.

A complete exercise training prescription should include, at a minimum, the frequency, mode, duration, and intensity of the exercise to be completed.[18] Frequency and duration refer to the number of exercise sessions per week, and length of individual sessions respectively. The mode of exercise refers to the type of exercise to be completed and is specific to the relevant fitness component. Intensity is reported in a number of different ways that vary according to the fitness component addressed. Ways of expressing the intensity of aerobic training prescriptions include the percentage of actual (as determined from fitness assessment) or predicted maximal oxygen consumption (VO_2max), maximal heart rate (HRmax), or heart rate reserve (HRR), or as a rating of perceived exertion (RPE). The intensity of resistance training prescriptions can be reported as a percentage of one-repetition maximum (1 RM), the amount of weight that can be lifted a specified number of times (e.g., 10 RM = maximum weight that can be lifted 10 times), or RPE.

In addition, three training principles should be applied when designing an exercise prescription: specificity, overload, and progression.[18] The principle of specificity suggests that to achieve a certain outcome from an exercise training program, it must be designed to address that particular outcome.[18] For example, to improve cardiorespiratory fitness, an aerobic training program would be most appropriate. Alternatively, if the goal is to improve muscular fitness, then a resistance training program should be prescribed. It is also important to note that for resistance and flexibility training, any improvement seen will be specific to the muscles or joints used. It is essential to address this principle and base the exercise program on the needs and goals of the cancer survivor to ensure that the desired results are achieved. The second principle, overload, requires that the exercise load must be greater than the body is accustomed to (i.e., greater than required for usual daily activities) for an adaptation (i.e., improvement) to occur.[18] For example, a moderate intensity walking program may be sufficient to improve cardiorespiratory in a sedentary individual. However, for a cancer survivor who is already active, this may not exceed usual daily activities, and cardiorespiratory fitness would not improve, unless the exercise stress was increased. The final training principle, progression, is similar to overload but refers to the long-term benefits of exercise training.[18] Although applying the overload principle correctly will result in fitness improvements, an exercise training program must gradually increase the volume of training to ensure that improvements continue to occur long-term. The proper application of all three training principles to an exercise prescription will help to maximize the health benefits for the cancer survivor.

Finally, it is important to structure each individual exercise session to include a warm-up, the exercise bout, and a cool-down.[18] The warm-up should consist of a general component of light aerobic exercise to gradual increase heart rate and body temperature, followed by a specific component of stretching for all muscle groups to be used during the exercise session. The warm-up may serve to reduce the risk of injury and enhance performance. The exercise bout itself requires the completion of the prescribed volume (time and intensity) and type of exercise. Specific exercise prescription guidelines to improve the health-related fitness components are provided below. The cool-down phase of each workout provides a recovery period from the workout by slowly decreasing the intensity of the activity. Stretching exercises should also be included at the end of the cool-down period. The cool-down allows for the body's systems to return to near-resting values and reduces the chances of cardiovascular events.

While evidence-based exercise guidelines are available for a number of chronic illnesses such as cardiovascular diseases,[22] type I and II diabetes,[100,101] chronic obstructive pulmonary disease,[102] and psychiatric diseases,[19] no such guidelines are available for cancer survivors.[60] Although no consensus on the appropriate exercise guidelines for cancer survivors has been reached, a number of sources have provided recommendations for prescribing exercise for this population.[60] Despite the lack of consensus on the volume and type of exercise that is optimal for cancer patients, it is likely that an exercise program aimed at maintaining or improving the health-related fitness components in cancer survivors would need to minimally meet the recommendations for maintaining or improving these variables in apparently healthy individuals. The Centre for Disease Control in conjunction with ACSM have suggested that individuals complete a minimum of 30 minutes of light to moderate physical activity on most (if not all) days of the week.[103] ACSM has since provided more specific guidelines to improve health-related fitness outcomes.[20] Table 3

Table 3. Summary of ACSM Guidelines for Maintaining or Improving Cardiorespiratory Fitness, Muscular Fitness, and Flexibility[20]

Fitness component	Training variable	Suggested prescription	Comments/suggestions
Cardiorespiratory	Frequency	3–5 days/week	
	Intensity	55/65–90% of VO_2max or HRmax 40/50–85% of HRR 12–16 RPE	Exercise duration will depend on intensity chosen (e.g., lower intensity exercise should be longer in duration, and vice versa)
	Duration	20–60 minutes	Exercise may be completed in smaller exercise bouts of 10 minutes throughout the day
	Type	Large muscle groups involved, continuous activity	Pick an activity that will be enjoyed
Muscular fitness	Frequency	2–3 days/week	At least 24 hours should be allowed between workouts of same muscle group
	Intensity	MS: 80–90% of 1 RM, ME: 60–70% of 1 RM 16 RPE (Prior to Failure) OR 19–20 RPE (Point of Fatigue) on last repetition	Ranges between those provided for MS and ME will benefit both aspects of muscular fitness, but not to the same extent as being trained alone
	Duration	1 set of 3–20 repetitions (MS: 3–8 repetitions; ME: 12–20 repetitions)	Rest periods between sets should increase with decreasing repetitions (i.e., increasing weight) Progression to multiple sets should be included if time allows
	Type	8–10 exercises to target major muscle groups	Should include core/stabilizing exercises in addition to upper and lower body exercises
Flexibility	Frequency	2–3 days/week (Preferably each day)	Can be included in the warm-up and cool-down phases of every workout
	Intensity	The muscle/joint should be stretched to a point of tension at the end of ROM	No pain should be felt throughout the entire ROM
	Duration	15–30 seconds/stretch 2–4 times/stretch	Stretches may be held for up to 1 minute
	Type	Slow and controlled static stretching for all major muscle groups	

HRR = heart rate reserve; VO_2max = maximal oxygen consumption; HRmax = maximum heart rate; RPE = rating of perceived exertion; MS = muscular strength; ME = Muscular endurance; 1 RM = one-repetition maximum; ROM = range of motion.

provides a summary of these guidelines along with some additional comments and suggestions to aid in their application. Additionally, ACSM has suggested exercise guidelines specific to improving and/or maintaining these health-related fitness components in older adults.[104] A comprehensive exercise program should be designed to include cardiorespiratory, resistance, and flexibility training.[18] Although the focus of the exercise prescription will vary according to each individual cancer survivor's needs, goals, and personal preferences, it is important that a training program attempts to maintain each fitness component at a minimum. Once exercise training has improved a fitness component to the desired level, it has been suggested that the maintenance of the exercise intensity will maintain that particular fitness component even with corresponding reductions in both frequency and duration.[18]

Cancer survivors initiating an exercise training program should begin at the lower end of the ranges provided for frequency, intensity, and time, when using the ACSM guidelines. It may be necessary to initiate an exercise program at levels lower than these recommendations depending on the individual's current medical status, treatment stage, and fitness/activity levels. In these cases, the volume of physical activity can be gradually progressed to meet the minimum guidelines. For any individual, progression should be gradual with no more than one variable increased at a time (e.g., intensity or duration, but not both).[97] Furthermore, specific contraindications and precautions for exercise have been outlined for cancer survivors who are currently receiving,[53] or have completed,[105] treatment, which should be considered in addition to those contraindications that are suggested for the general population.[18,99]

9.0. FUTURE RESEARCH

In 2001, Courneya and Friedenreich published the PEACE (Physical Exercise Across the Cancer Experience) framework, providing a broad structure within which research on physical activity and cancer could be organized and planned.[106] The framework breaks down the cancer experience into six phases: two prediagnosis (prescreening and screening) and four postdiagnosis (pretreatment, treatment, posttreatment, and resumption), and identifies eight cancer control outcomes that may be influenced by exercise during the different phases. For some of these outcomes, studies have already been published or are underway. For others there is little previous or current research. The framework helps locate the gaps in the evidence base, thereby providing directions for future investigation (see Figure 1).

During the prescreening time period, the outcome of interest is primary prevention of cancer. There is already a sizable body of data on the role of exercise in cancer protection, and continued research will help to define more clearly the amounts and types of activity required to reduce risk at specific cancer sites, and to understand the mechanisms underlying the protective effects.

In relation to screening, there may be potential for physical activity to compromise the validity of screening tests, hence interfering with cancer detection. Several studies have investigated the effect of cycling on blood concentrations of prostate specific antigen (PSA), which is used in diagnostic testing for prostate cancer. Although some cases of elevated PSA concentrations after cycling have been reported, other studies have found no change, and the issue is unresolved.[107] A further possible area of investigation in relation to physical activity and detection is a potential role of exercise in helping to reduce anxiety associated with screening tests and results.

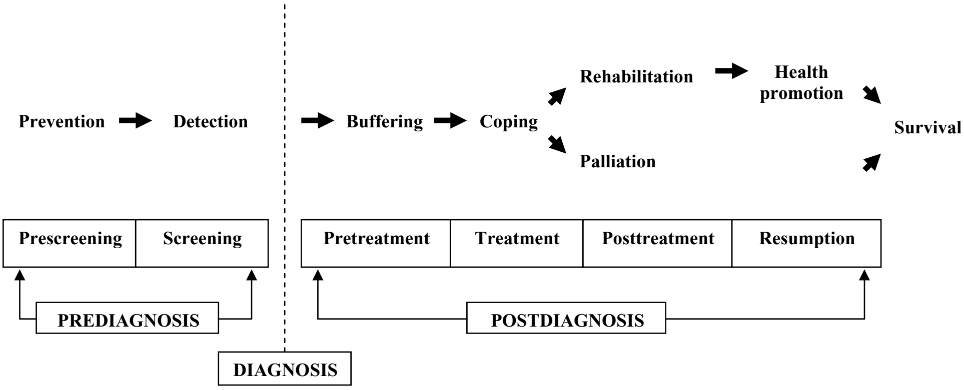

Figure 1. Framework PEACE: An Organizational Model for Examining Physical Exercise Across the Cancer Experience. Reprinted with permission from Courneya KS. and Friedenreich CM[106]

In the pretreatment phase, a potential buffering role of exercise has been identified where improving fitness prior to commencing therapy, may allow patients to better withstand aggressive treatments. Little research has focused on this question so far.

During treatment, interest in the impact of exercise is focused on coping outcomes. As discussed earlier in this chapter, existing research has provided preliminary data that physical activity has positive effects on various functional and quality of life outcomes in cancer survivors during therapy. Although the bulk of the data relates to women with breast cancer, there are an increasing number of trials investigating other cancer populations. Researchers are also trying to address questions regarding the different dimensions of exercise interventions (e.g., type, frequency, intensity) in order to optimize coping benefits for patients.

During the posttreatment phase, principal outcomes relate either to rehabilitation, with the aim of restoring successfully treated patients as far as possible to normal function and well-being, or to palliation where the purpose is to alleviate the symptoms of those patients who cannot be cured. Relatively few exercise trials have targeted this time period so far, with most concentrating on either patients receiving active treatment or long-term survivors.

The final phase defined in the PEACE framework is resumption, during which the potential value of physical activity is for health promotion purposes, similar to the general population. Several studies have reported that physical activity levels among cancer survivors are lower than they were before diagnosis,[108–110] although one large study suggested that the numbers of survivors meeting recommended activity guidelines were similar to individuals without a history of cancer.[111] A recent review suggested that cancer diagnosis may represent a teachable moment for promoting positive lifestyle changes such as increased activity, that contribute to improved health and well-being.[56] As discussed in the earlier chapter on exercise motivation and behavior change, there are a number of ongoing studies testing interventions targeting exercise behavior change in cancer survivors.

The last cancer control outcome identified that might be related to exercise is survival. The preliminary data discussed earlier in this chapter are encouraging with respect to exercise contributing to increased survival for breast and colorectal cancer,[29,31] and further studies of this kind will provide additional information about the value of exercise on this important outcome.

10.0. CONCLUSION

In summary, research activity in the field of physical exercise and cancer is thriving. There is a growing body of evidence indicating a positive effect of physical activity in the primary prevention of cancer. Although only limited data are presently available regarding the potential of exercise to prevent recurrence and increase survival, preliminary findings are encouraging. There are a number of trials to support recommendations that cancer patients should remain physically active during cancer treatment in order to preserve fitness and function, and retain independence in performing activities of daily living. Furthermore, physical activity is an important part of health promotion among cancer survivors for encouraging positive lifestyle changes that contribute to optimizing health and well-being. Finally, ongoing research is attempting to fill current gaps in the evidence base with the aim of enhancing the understanding of the effects of exercise on cancer control outcomes across the entire cancer experience from prevention, through treatment, recovery or palliation, toward long-term survivorship.

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Chapter 15

Nutrition and Weight Management in Cancer Survivors

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1.0. BODY WEIGHT AND CANCER

The prevalence of obesity has become an epidemic. It is estimated that in the United States, 64.5% of the general population is either overweight, defined by body mass index [BMI, body weight (kg)/height $(m)^2$] between 25.0 and 29.9 kg/m^2, or obese (BMI > 30.0 kg/m^2).[1] The major medical complications associated with obesity include metabolic syndrome, type 2 diabetes, cardiovascular disease, hypertension, and certain types of cancer,[2] to name a few. Cancers strongly associated with obesity include kidney, esophagus, colon, gallbladder, pancreas, endometrial, ovary, and postmenopausal breast cancer.[3,4]

There are several potential mechanisms connecting obesity with the increased risk of cancer:

(1) Elevated blood estrogen levels. Adipose tissue is an extragonadal source of estrogen that can convert androgen into estrogen. With large amounts of adipose tissue mass in obese individuals, the amount of estrogen circulating in these individuals is higher than normal. Estrogen is known to stimulate tumorigenesis and thus increase the risk of cancer, especially estrogen receptor (ER)-positive breast cancer.[5,6]

(2) Hyperinsulinemia/insulin resistance. Hyperinsulinemia and insulin resistance are the cornerstones of metabolic syndrome and are commonly seen in obese individuals.[7] Hyperinsulinemia/insulin resistance reduces the production of insulin-like-growth factor binding protein-1 (IGFBP-1) and IGFBP-2, thus increases the level of free insulin-like growth factor-1 (IGF-1).[8] Insulin and IGF-1 are known to stimulate mitogenesis and angiogenesis and therefore may increase the risk of cancer.[8–10] In addition, hyperinsulinemia is correlated with reduced production of sex hormone-binding globulin.[11] The net effect of increased estrogen production and reduced sex

hormone-binding globulin production is elevated levels of free estrogen in blood circulation. As a result, the risk for breast cancer is increased. Patients with metabolic syndrome or elevated levels of insulin and IGF-1 also have an increased risk for colon cancer.[12,13] Other metabolic abnormalities observed in obesity as part of the metabolic syndrome include high levels of total cholesterol, low-density-lipoprotein cholesterol (LDL-C) and triglyceride, low levels of high-density-lipoprotein cholesterol (HDL-C), and hypertension.[7] A low HDL-C has been shown to be associated with high levels of blood estrogen, leptin, and insulin, and thus may serve as a marker for breast cancer risks in postmenopausal women.[14–16]

(3) Other metabolic alterations. Obesity is characterized with elevated blood leptin levels.[17,18] Leptin, the protein product of the ob gene, is secreted by adipose tissue and is directly correlated to total adipose tissue mass in the body.[18] Leptin has been reported to be angiogenic[19,20] and has been postulated to be the link between obesity and prostate cancer,[21,22] breast cancer,[23,24] colon cancer,[25] as well as cancer in other sites.[26]

2.0. BODY WEIGHT AND CANCER RECURRENCE

Obesity is not only a risk factor for cancer occurrence, but also a risk factor for cancer recurrence,[27,28] poor prognosis for survival,[29–33] and increased risk of cancer mortality.[34] Weight gain after diagnosis can also adversely affect cancer prognosis and survival.[33] Weight gain is common in breast cancer patients, especially in those who are receiving adjuvant chemotherapy or are younger than 60 years of age.[35–37] This weight gain after breast cancer diagnosis may be attributed to reduced physical activity[38] and altered dietary patterns.[39] It is interesting to note that some studies did not detect a change in body weight. However, a change in body composition, mainly an increase in adipose tissue mass and reduction or no change in lean body mass, has been observed in these studies.[40,41]

3.0. DIETARY INTERVENTION AND BODY WEIGHT CHANGES IN CANCER SURVIVORS

With a poorer prognosis for survival, it is expected that obese cancer survivors should have enhanced motivation to lose weight in order to prevent cancer recurrence or to prolong cancer-free life. Different dietary regimens have been deployed to assist cancer survivors in losing weight. Dietary intervention trials aimed at increased intakes of fruit, vegetable, and fiber, and reduced fat intake were usually effective in achieving short-term goals, and resulted in weight loss during the first 6 months of the trial.[42] However, the long-term effectiveness of these interventions is debatable. Thomson *et al.* reported that at the end of 4 years, the body weight, BMI, and body composition of the breast cancer survivors were not significantly different from the baseline levels.[43] Thus, even though the intakes of fruit, vegetable, and fiber were still increased compared to baseline level, reduction in energy intake is still necessary in order to maintain the weight loss observed during the early post-diagnostic period.[44] In a population-based study, Coups and Ostroff reported that without any intervention, there was no difference in dietary intake patterns in terms of fruit, vegetable, and fat intakes between cancer survivors and non-cancer controls.[45] However, Blanchard *et al.* reported that 47% of the cancer survivors did improve their dietary quality.[44,46]

We have employed different weight loss regimens to compare the effectiveness of weight loss and maintenance in breast cancer survivors.[47,48] In this study, the participants were randomized into four treatment groups:

(1) Control group: Participants were only given the National Cancer Institute's "Action Guide to Healthy Eating" and the "Food Guide Pyramid" without any other dietary or exercise instruction;
(2) Weight Watchers group: Participants were provided with free coupons to attend weekly Weight Watchers group meetings with no further dietary or exercise instructions;
(3) Individualized group: Participants met with a registered dietitian (RD) for weekly one-on-one counseling for the first 3 months, biweekly for the next 3 months, and monthly for the last 6 months. They were free to call the RD at any time if they need more nutritional counseling. They were required to keep diet and exercise records; and
(4) Comprehensive group: Participants in this group were provided with free coupons to attend Weight Watchers weekly meetings and also received individualized dietary counseling. They were required to keep diet and exercise records.

At the end of 12 months, the three intervention groups lost weight. However, only the Individualized and Comprehensive groups had statistically significant weight loss as compared to their baseline weight (Table 1), and only the Comprehensive group reduced a significant amount of body fat percent. Participants in the Comprehensive group also showed the most improvement in metabolic parameters, such as an increase in HDL-C and reduction in LDL-C and leptin levels. Thus, even in breast cancer survivors for whom losing weight is beneficial, it is unlikely that weight loss will be achieved without any intervention. Furthermore, it appears that intensive individualized diet counseling and group support are required to achieve significant weight loss. Demark-Wahnefried *et al.* also reported that to date, all the dietary interventions were resource intensive.[49] In addition, dietary interventions may achieve the goal of increasing fruit and vegetable intake and reducing fat intake in

Table 1. Anthropometric and Dietary Changes from Baseline to the End of 12 Months of four Groups of Subjects

	Control	Weight watchers	Individualized	Comprehensive	p
Body weight (kg)	1.1 ± 1.7^{a}	-2.7 ± 2.1^{ac}	$-8.0 \pm 1.9^{bc*}$	$-9.5 \pm 2.7^{b*}$	<0.005
BMI (kg/m^2)	0.5 ± 0.9^{a}	-1.5 ± 1.0^{ac}	$-3.0 \pm 1.3^{bc*}$	$-3.7 \pm 0.8^{bc*}$	<0.005
Body fat (%)	0.23 ± 0.6^{a}	-0.99 ± 0.08^{ac}	-3.17 ± 0.8^{bc}	-3.65 ± 1.1^{bf}	<0.05
Energy intake (kcal)	-145 ± 179	-570 ± 58^{f}	$-515 \pm 118^{*}$	$-393 \pm 163^{*}$	ns
Dietary fat intake (%)	$5.4 \pm 3.7^{*}$	$-2.6 \pm 2.8^{*}$	$-4.8 \pm 1.5^{*}$	0.9 ± 3.4	ns

Adopted from Jen *et al.*[47] with permission. Numbers with different superscripts were significantly different from each other.

*Significantly different from its baseline value at $p < 0.05$; f significantly different from its baseline value at $p < 0.01$; ns, not significant.

breast cancer survivors, but without energy restriction, weight loss is still not likely to be achieved.[43]

Since weight loss can prevent cancer incidence and recurrence, as well as other chronic diseases,[50] weight loss has been attempted by obese individuals as well as cancer survivors. However, weight loss maintenance is very difficult to achieve. It has been reported that less than 10% of formerly obese patients are able to maintain significant weight loss for an extended period of time, and weight regain is fast.[51] For many obese individuals, this weight loss/regain cycle repeats many times thus producing a weight yo-yo or weight cycling phenomena. We have previously reported that animals experiencing this kind of weight cycling showed insulin resistance.[52] Moreover, at sacrifice time, animals which went through five cycles of weight cycling had similar body weights as the control animals that maintained a constant body weight throughout the study.[53] However, the weight-cycled rats still had elevated levels of 5-hydroxymethyl-2'-deoxyuridine as compared to the control animals. 5-hydroxymethyl-2'-deoxyuridine, an oxidized thymidine residue, is an indicator of oxidized DNA damage and serves as a marker for breast cancer risk.[54] Thus, these animal data indicated the potential of weight cycling to induce breast cancer. However, we also observed that when insulin resistance was not produced, weight cycling did not increase the risk of breast cancer.[55] Therefore, it may be the insulin resistance per se, not the weight cycling itself, that increases cancer risks. Cleary *et al.* reported that weight cycling reduced the incidence of mammary tumors.[56] However, no data on insulin resistance in these mice were reported. It is possible that no insulin resistance was produced in their animals as judged by the fact that weight-cycled mice had similar body weight, fat pad weight, and IGF-1 levels as the ad-libitum fed mice. Since weight gain/obesity is positively associated with insulin resistance and weight loss improves insulin sensitivity, weight loss or maintenance should be strongly encouraged in cancer survivors.

4.0. STRATEGIES FOR WEIGHT LOSS

Body weight regulation is determined by energy balance: energy intake and energy expenditure. In order to lose weight, a negative energy balance (energy intake less than energy expenditure) must be achieved. Generally speaking, there are two dietary strategies to reduce energy intake: (1) altering dietary composition; and (2) reducing food intake and eating a balanced diet, thus reducing energy intake.

5.0. ALTERING DIETARY COMPOSITION

5.1. Low Carbohydrate (CHO), High Protein/Fat Diets

This type of diet has enjoyed widespread popularity in recent years. The most famous representatives of this type are “Dr. Atkin’s Diet Revolution” in the 1970s and his “Dr. Atkin’s New Diet Revolution” in the 1990s. This type of diet proclaims that high CHO induces postprandial hyperglycemia, and thus elevates insulin secretion. This increased insulin secretion not only enhances lipogenesis by increasing glucose uptake by the fat cells, but also triggers hunger due to reduced blood glucose levels.[57–59] In addition, elevated insulin levels inhibit the release of the brain satiety hormone serotonin.[60] Thus, consuming a high CHO diet will make individuals even hungrier and desire to eat even more CHO, and the elevated blood insulin levels will cause insulin resistance.[57–59] As stated previously, insulin resistance reduces the secretion of sex hormone binding globulin and IGFBP-1, thus producing more free-circulating IGF and estrogen. As a result, cancer risk is increased. The low CHO diets claim that by reducing CHO intake, blood insulin secretion will be blunted and the possibility of insulin resistance will be reduced. When individuals start a low CHO diet, weight loss is faster when compared to individuals on a high CHO diet at the end of 6 months. At the end of 1 year, the amount of weight lost is similar for people on the high and low CHO diets.[61,62] The rapid weight loss at the beginning of a low CHO diet is mostly due to loss of body water and muscle and liver glycogen. A significantly higher amount of lean body mass loss has also been observed with low CHO/high fat diet as compared to high CHO/low fat diet.[63] Low CHO diets also generate ketones because of incomplete fat catabolism.[64] Ketones may suppress appetite, a mechanism proposed by Atkins as desirable. Nevertheless, the long-term health effects of elevated ketone levels in adults have not been examined.[65]

The effects of a low CHO diet on appetite depend on whether the diet is high in fat or protein. A reduction in perceived hunger from baseline levels in individuals consuming the low CHO/high protein diet, but not the high CHO diet, for 6 weeks has been observed.[66] However, the long-term effects of a low CHO/high protein diet on hunger perception warrants further investigation. High fat diets, on the other hand, have weak satiety value, and thus may lead to overconsumption.[67] The long-term consequence of consuming a high fat diet could be increased weight gain and obesity.

The improvement of blood triglyceride and HDL-C seen in individuals on the low CHO diets has been proclaimed as evidence that a low CHO diet is superior to a high CHO diet.[61,62] This improvement may be explained by the weight loss. Since individuals consuming low CHO diets lost more weight at the beginning of the diet,[61,68] it is not surprising to see a better lipid profile than that of people on a high CHO diet. However, a low CHO diet can also result in increased total cholesterol and LDL-C levels.[61,68,69] Therefore, the health benefit of long-term consumption of this type of diet is still questionable.

Other adverse effects of low CHO diets include increased urinary calcium excretion,[70] foul taste in the mouth,[71] weakness,[71] constipation,[72] and headache and dizziness,[73] to name a few. Many of these symptoms are similar to those cancer survivors reported during and/or following radiation and various types of chemotherapy.[74,75] Increased urinary calcium excretion may increase the risk of developing osteoporosis.[76] Treatment for breast and prostate cancer will also increase the risk of osteoporosis,[77] suggesting that a high protein/fat diet may be contraindicated for cancer survivors. However, we have observed that in postmenopausal women, breast cancer survivors had significantly higher proximal radial Z scores (age and ethnicity-adjusted bone density) than controls while there was no difference between cases and controls in premenopausal women.[78] The Z score was also significantly higher in African American cases than in African American women in the control group. No such difference was identified in Caucasian women.[78] These inconsistent results point to the need for further study to examine the relationship between high protein/fat intake, osteoporosis and cancer occurrence and recurrence. Before a definitive answer is derived, it would be a good practice not to consume a high protein/fat diet because of its association with other chronic diseases.

High protein/fat diets allow for unlimited quantities of meat, cheese, eggs, and other high protein/fat foods while severely restricting fruit and vegetable intakes. Yang *et al.*[79] reported that in Japan, the incidence of colorectal cancer was positively correlated with the intakes of animal protein, fat, and oil, but was negatively associated with plant protein consumption. High fat/high protein diets are also correlated with renal cell carcinoma.[80] Nagle *et al.*[81] observed that cancer survival was negatively associated with the intake of red meat, white meat, and protein, but positively correlated with vegetable intake, especially cruciferous vegetables.

Even though there is no research specifically examining the relationship between high fat/protein intake and cancer recurrence at this point, given the fact that cancer patients are more likely to develop other chronic diseases[82] that are associated with high fat/protein intake, it seems advisable for the cancer survivors to avoid diets high in protein or fat.

5.2. High CHO Diets

High CHO diets have moderate protein content and low fat content (usually between 10 and 20%). The representative diets are Dr. Pritikin's diet[83,84] and Ornish's diet.[85,86] Barnard[87] reported that for subjects who were in the Pritikin Longevity Center for 3 weeks, medically supervised with daily aerobic exercise, and fed the Pritikin diet, there was a 5.5% decrease in body weight in men and a 4.4% decrease in women.[87,88] However, Barnard's studies omit information on total caloric intake or energy expenditure. Pritikin did recommend 1000–1200 kcal/day, which would suggest that they consumed a low-calorie diet. Ornish *et al.*[89] reported that results from the Lifestyle Heart Trial indicated that there was a significant difference in the amount of fat intake and weight loss between the experimental group following the Ornish diet and their Control group: 10.9 kg weight loss at 1 year with a sustained weight loss of 5.8 kg at 5 years in the experimental group, compared to no change in the control group. Havel *et al.*[90] reported that for women with a family history of diabetes, consumption of a low fat diet for 6 months was predictive of weight loss and fat loss. A meta-analysis conducted by Astrup *et al.* revealed that an ad-libitum low fat/high CHO diet induced a significant weight loss.[91] It is worth mentioning that many of the studies examining the effects of a low fat/high CHO diet on body weight regulation observed a reduction in energy intake, even though energy reduction was never intended.[92,91] Thus, one advantage of the high CHO diets is lowered energy intake due to low energy density in this type of diet.

However, not all studies have reported a greater weight loss for individuals on high CHO diets as compared to those on conventional low caloric diets or low CHO diets.[61] Nordmann *et al.* analyzed five randomized clinical trials comparing low CHO versus high CHO diets. They concluded that after 6 months, individuals randomized to the low CHO diet lost more weight than those randomized to low fat/high CHO diet.[93] Nevertheless, the difference between the diets disappeared at the end of 1 year.

The major focus of this dietary approach is to focus on the "type" of calories and "caloric density" rather than "counting total calories" directly. The focus is really based on the promotion of eating more high complex carbohydrates and high fiber foods to lose weight—specially to eat more fruits, vegetables, whole grains, and beans, while trying to omit sugar and white flour (note: Ornish's diet is vegetarian, while Pritikin allows for a limited amount of low fat animal protein daily: no more than 3.5 ounces/day).[94] Foods high in fruits and vegetables are usually low in energy density.[95] The energy densities of foods have been shown to be associated with body weight and BMI.[95,96] It has been reported that overweight subjects who consume a low fat, high CHO diet do eat fewer calories and lose weight and body fat.[68, 90, 97–99] Nevertheless, Raben *et al.*[100] and Prewitt *et al.*[101] both reported that the consumption of a low fat diet resulted in an increase in caloric intake but a decrease in body weight. Hays *et al.*[102] reported that a diet rich in complex carbohydrates resulted in an increase in lean body mass and a decrease in fat mass among 34 subjects with impaired glucose tolerance.

The Iowa Women's Health Study has observed that postmenopausal women who were less overweight and consumed less fat had higher rate of survival after breast cancer diagnosis than those who were overweight and consuming higher fat.[103] In order to evaluate the efficacy of a low fat/high complex CHO diet on breast cancer recurrence, two multicenter randomized controlled trials of dietary interventions have been funded by the National Cancer Institute: the Women's Intervention Nutrition Study (WINS) and the Women's Healthy Eating and Living Study (WHELS). The Women's Healthy Eating and Living Study is a part of the Women's Health Initiative. The WINS study was designed to investigate the effects of reducing dietary fat intake with adjuvant systemic therapy on cancer recurrence rates in postmenopausal women with early stage, surgically treated breast cancer.[104] The primary aim of the WHELS is to evaluate the effects of a high-vegetable, low fat diet in reducing breast cancer recurrence and mortality.[105] Although weight loss was not the goal of these programs, some weight loss in the intervention groups have been observed in some reports[106,107] although not in others.[43,44]

There have been concerns regarding the impact of the consumption of high CHO, low fat diets on blood glucose, lipids, insulin, and leptin levels. Most studies have reported that these diets usually result in decreased energy intake, blood glucose, and insulin levels.[84,88,108,109] The effects of high CHO diets on blood lipid levels are controversial. Gerhard *et al.* reported that a low fat/high CHO diet significantly reduced body weight as compared to a diet high in monounsaturated fat diet. However, there was no difference between these diets in the levels of blood lipids nor in glycemic control and insulin sensitivity.[110] On the other hand, high CHO diets have been reported to increase blood triglyceride levels.[61,62,68] Noakes *et al.* reported that individuals on an energy-restricted, high-protein diet had metabolic profiles as good as or even better than those on a high CHO diet.[109] Kasim-Karakas *et al.* observed that when individuals on an high CHO diet ad-libitum, they lost weight but maintained their normal blood triglyceride levels.[99] However, when individuals were put on an euenergetic high CHO diet to maintain their body weight, their blood triglyceride levels elevated. Similar findings have been noticed by others. Schaefer *et al.* reported that effects of a high CHO diet on blood lipid levels were related to the body weight change.[111] When body weight was kept constant, the high CHO diet lowered total cholesterol, LDL-C, and HDL-C, as well as elevated triglyceride levels. When the high CHO diet was consumed ad-libitum, these individuals lost weight and lowered their LDL-C without any adverse effects on blood triglyceride levels and TC/HDL-C ratios.[111] Thus, the effects of high CHO diets can be modulated by the energy intake or body weight change.

Many of the controversies regarding the effects of high CHO diets on blood lipid levels may also be related to the CHO used. When high CHO diets are high in fruits and vegetables (and thus are high in fiber), the diet's adverse effects on blood lipid levels may be alleviated.[112,113] Many of the "low fat" food products on the market, on the other hand, are high in simple CHO, as demonstrated in Table 2.

Table 2. Energy and Macronutrient Content of Regular and Fat-Reduced Peanut Butter of a National Brand (Serving Size: 2 Tablespoons)

	Regular fat	Reduced fat
Energy (kcal)	190	190
Fat (g)	16	12
Fat (kcal)	130	110
Carbohydrate (g)	6	15
Sugar (g)	2	4
Protein (g)	8	8

With the added simple CHO, there is no reduction in caloric content, even though the fat content is reduced. The added simple CHO also elevates blood lipid levels. Thus, these "reduced-fat" products offer no health benefits. Considering the fact that the current dietary guidelines for cancer prevention include a high consumption of fruits and vegetables and a reduced intake of fat,[114] the low fat, high CHO diets rich in fruits and vegetables should also be recommended for cancer survivors and for all individuals in order to reduce the risks for other chronic diseases.

Studies investigating the satiety of high CHO, low fat diets have reported that low fat diets received higher hedonic ratings compared to high-fat diets.[98] The exposure to high CHO containing foods can result in a marked restraining effect on the expression of appetite.[115]

There are data to support that individuals who consume a low fat, high CHO diet are perhaps more successful at maintaining weight loss.[116–118] The responses of insulin and leptin levels to dietary CHO may play a role in the weight-maintaining effects of these dietary regimens. Weigle *et al.*[119] have reported that there was no difference in the area under the curve (AUC) for blood leptin levels between high CHO and low CHO diet consumption in the short-term. However, after 12 weeks on the high CHO diet, the AUC for leptin in that group was significantly higher than that observed for the low CHO diet. Therefore, one of the mechanisms for the maintenance of weight loss in high CHO diets may be attributed to the elevated leptin levels.

5.3. Balanced, Energy-Reduced Diets

Diets in this category are represented by the Dietary Approaches for the Stop of Hypertension (DASH) diet,[120] the National Cholesterol Education Program Step I Diet (NCEP),[121] and the 2002 National Academy of Science's Institute of Medicine (IOM) dietary guidelines.[122] Several studies have reported that total caloric content was more important than diet composition for weight loss,[123,124] and the percent of calories from fat (15–35%) did not seem to influence the amount of weight loss. Based on the analysis of four popular diets with very different diet compositions by Dansinger *et al.*,[69] it is apparent that there is not one specific macronutrient that induces weight loss. Rather, it is the reduction in total energy intake and the degree of adherence to the diet that produces the weight loss. Without reduction in energy intake, even diets with high fruits and vegetable content would not achieve weight loss.[43,44] The best strategy to reduce energy intake is to reduce portion size and to reduce the consumption of energy-dense foods.

Since the degree of adherence determines the amount of weight loss, the best diet to reduce body weight would be a diet that is nutritionally balanced and easy

Table 3. Low-Calorie Step I Diet to Reduce Body Weight in Obese Individuals[125]

Nutrient	Recommended intake
Calories	Approximately a 500 to 1000 kcal/day reduction from usual intake
Total fat	30% or less
Saturated fatty acids	8–10% of total calories
Monounsaturated fatty acids	Up to 15% of total calories
Polyunsaturated fatty acids	Up to 10% of total calories
Cholesterol	<300 mg/day
Protein	Approximately 15% of total calories
Carbohydrate	55% or more of total calories
Sodium chloride	No more than 1000 mmol/mol/day (approximately 2.4 g of sodium or 6 g sodium chloride)
Calcium	1000–1500 mg/day
Fiber	20–30 mg/day

to adhere to for long periods of time. A diet that severely restricts one type of food to the extreme may produce desired short-term weight loss, but long-term success may be difficult to achieve.[69] Dietary recommendations for weight loss should be based on the "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults."[125] The key element of these guidelines is the use of a moderate decrease in caloric intake to achieve a slow but progressive weight loss. The dietary composition goals of these guidelines are shown in Table 3. Another recommendation for a balanced, low-energy diet plan is the USDA's Dietary Guidelines for Americans 2005 (http://www.healthierus.gov/dietaryguidelines/) which include adopting a balanced eating plan based on the USDA Food Guide or the DASH eating plan (Table 4). The DASH diet emphasizes fruits, vegetables, and low fat dairy products. American Institute for Cancer Research also established "AICR Diet and Health Guidelines for Cancer Prevention" which again emphasizes choosing plant-based diet plans, consuming plenty of fruits and vegetables, and maintaining a healthy body weight, among other recommendations (http://www.aicr.org/site/PageServer?pagename=home_guides, http://www.aicr.org/site/PageServer?pagename=cs_guidelines).

From the research evidence collected thus far, it is clear that in order to prevent cancer occurrence/recurrence, maintaining a healthy body weight and consuming enough fresh fruits and vegetables are critical. Therefore, the optimal dietary plan would be to follow the NCEP's Step I diet plan. The goals of this diet plan are as follows.

Table 4. The DASH Diet Recommendations

Type of food	Number of servings for 1600–3100 kcal diets
Grains and grain products (include at least three whole grain foods each day)	6–12
Fruits	4–6
Vegetables	4–6
Low fat or nonfat dairy foods	2–4
Lean meats, fish, poultry	1.5–2.5
Nuts, seeds, and legumes	3–6 per week
Fats and sweets	2–4

(1) To reduce energy intake. By reducing energy intake by 500 kcal to 1000 kcal, a weight loss of 1 to 2 lb/week will be produced, since a pound of fat is about 3500 kcal. This reduction in energy intake can be easily achieved by reducing the portion size without any major alteration in eating plan. The portion sizes for commonly consumed foods are presented in Table 5.

(2) To reduce daily fat intake to about 30% of energy intake, to replace saturated fatty acids with mono or polyunsaturated fatty acids, and to reduce cholesterol intake. It has been shown that not only the quantity but also the quality of dietary fat is important for general health. Saturated fats and trans fats are associated with hyperinsulinemia and insulin resistance, which could in turn increase the risk for cancer.[126,127] Omega-3 (ω-3) fatty acids improve insulin sensitivity, and thus may reduce cancer risk.[128,129] However, a recent meta-analysis of the effects of dietary fatty acids on cancer risks showed no consistent connection between ω-3 fatty acids and cancer incidence.[130] Nevertheless, considering the fact that cancer patients are at higher risk of other chronic diseases and ω-3 fatty acids are known to be protective of cardiovascular diseases,[127,131] replacing saturated fatty acids with ω-3 fatty acids may still be advisable. Foods rich in ω-3 fatty acids are fatty fish such as mackerel, salmon, herring, tuna, as well as canola and soybean oils, walnuts, flaxseeds.

Table 5. USDA's Daily Food Guide and Serving Sizes[134]

Bread, Cereals, and other grain products: 6 to 11 servings/day
One serving: 1 slice bread
½ cup cooked cereal, rice or pasta (looks like ½ baseball)
1 oz ready-to-eat cereal
½ bun, bagel or English muffin
1 small roll, biscuit, or muffin
3 to 4 small or 2 large crackers
Vegetables: 3 to 5 servings/day
One serving: ½ cup cooked or raw vegetables (looks like ½ baseball or rounded handful for adult)
1 cup leafy raw vegetable (looks like 1 baseball or fist of an average adult)
½ cup cooked legumes
¾ cup vegetable juice
Fruits: 2 to 4 servings/day
One serving: 1 medium apple, banana, or orange (looks like a baseball)
½ grape fruit
1 melon wedge
¾ cup juice
½ cup berries
½ cup diced, cooked, or canned fruit
¼ cup dried fruit (looks like 1 golf ball)
Meat, poultry, fish, and alternates: 2 to 3 servings/day
One serving: 2 to 3 oz lean, cooked meat, poultry, or fish (looks like a deck of cards)
1 egg
½ cup cooked legumes (looks like ½ baseball)
4 oz tofu
⅓ cup nuts or seeds (level handful for average adult)
2 tablespoons peanut butter (as 1 oz meat, look like a marshmallow)
Milk, cheese, and yogurt: 2 servings/day
One serving: 1 cup milk or yogurt
2 oz processed cheese food
1 ½ oz cheese (1 oz looks like 4 dice)

(3) To consume plant-based protein and lean meats as the main protein source of the diet. These types of foods contain no or low amount of cholesterol and saturated fatty acids. They not only provide adequate amount of protein, but also reduce the risk of cardiovascular disease and cancers.

(4) To use complex carbohydrates, such as fruits, vegetables, and whole grains as the carbohydrate sources as suggested for the DASH diet.[125] These complex carbohydrates contain not only adequate amounts of fibers, but also micronutrients that have been shown to reduce cancer risk.[129] These micronutrients include vitamins C and E, folate, carotinoids, calcium, and phytochemicals. Consuming whole foods is preferable over supplements, since the micronutrients in whole foods may have synergistic effects to provide maximal protection. Foods rich in the colors red (tomatoes, red peppers, red onions, beets, strawberries, raspberries, watermelon, etc), green (broccoli, green leafy vegetables, green pepper, green grapes, honey dew, etc), blue/purple (blueberries, blackberries, eggplant, purple grapes, etc), orange/yellow (carrots, pumpkin, sweet corn, butternut squash, sweet potatoes, oranges, cantaloupes, nectarines, papayas, etc) and white (cauliflower, onions, garlic, potatoes, mushrooms, pears, bananas, etc) are the best sources of these micronutrients and are strongly recommended to reduce the risk of cancer occurrence and recurrence. For more detailed fruit and vegetable choices, please visit http://www.5aday.org/html/colorway/colorway_home.php. If fresh fruits and vegetables are not readily available, frozen or canned varieties are suitable substitutes.[132] For some cancer survivors with compromised immune systems, consuming raw vegetables may not be advisable[132] because the pathogens attached to these foods may increase the risk of infection.

In summary, evidence suggests that in order to reduce the risk of cancer recurrence, cancer survivors should try to maintain a healthy body weight. Obese cancer survivors should follow the NCEP's Step I diet to reduce energy intake and thus body weight. Following the DASH diet simultaneously will ascertain that adequate fruits and vegetables are consumed to take advantage of the phytochemicals and dietary fibers contained in this type of diet in order to reduce the risk of cancer occurrence/recurrence.

The other side of the equation for body weight regulation is energy expenditure. The major components of energy expenditure are basal metabolic rate, the thermic effects of foods (energy used to process food consumed), and physical activity. The only component of energy expenditure that individuals have control over is physical activity. How physical activity can reduce the risk of cancer and prevent cancer recurrence is presented in Chapter 15 of this book.

6.0. FUTURE RESEARCH NEEDS

Major strides have been made in identifying the mechanisms of carcinogenesis and effective treatment regimens. Coupled with early detection, cancer mortality rates have been declining continuously.[133] As a result, the number of cancer survivors has increased significantly. However, there are major gaps in the knowledge regarding the long-term efficacy of dietary regimen to prevent cancer recurrence and/or prolong cancer-free life. Future research in nutrition and cancer survivors should be focused on the following as summarized in Table 6.

Table 6. Future Research Needs for Cancer Survivors

Needs	Goals
To collect long-term data from dietary intervention trials	To establish that Step 1 diet and DASH diet are effective in weight loss and maintenance, and in preventing cancer occurrence/recurrence
To develop plans to disseminate nutrition knowledge about high CHO/low fat diets	To make general public and cancer survivors aware the health benefits of the high CHO/low fat diets and how to adhere to these dietary plans
To establish policies to make fresh fruits and vegetables and whole grain foods available and affordable	To make fresh fruits, vegetables and whole grain foods the major component of daily meals
To encourage a healthy lifestyle	To use nutritional and behavioral strategies to reduce the risk of cancer occurrence/recurrence

(1) Collecting data from long-term dietary intervention trials to further establish the efficacy of Step I diet plus DASH diet (low fat/high CHO rich in complex CHO) in cancer survivors (as well as general public) on reducing body weight and maintaining the weight loss, as well as on preventing cancer recurrence. These dietary plans have to be innovative and easy to follow so individuals can adhere to them for a lifetime. The AICR's "The New American Plate" (http://www.aicr.org/site/PageServer?pagename=pub_nap_index_21) is one of the fresh and easy ways to help individuals to consume more plant-based foods.
(2) Developing plans to disseminate knowledge regarding the health benefits of high CHO/low fat diets to general public, especially to cancer survivors.
(3) Establishing policies to make fresh fruits and vegetables, and whole grain foods readily available and affordable to the general public.
(4) Encouraging cancer survivors and general public to follow a healthy lifestyle, including maintaining a healthy body weight, consuming a balanced, plant-based diet with reduced energy intake, and engaging in daily physical activities.

Since the Step I diet and DASH diet have been proven to be safe and less expensive than drugs, consuming these diets may prove to be a viable alternative for reducing the risk of cancer occurrence/recurrence.

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Chapter 16

Management of Chemotherapy-Related Cognitive Dysfunction

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1.0. BACKGROUND

Dysfunction in memory and attention associated with cancer treatment has gained increased attention over the past two decades. In 1999 the President's Cancer Panel[1] and the National Coalition for Cancer Survivorship[2] formally recognized the problem as a quality of life matter that deserved higher priority in clinical research. With nearly 1 million chemotherapy recipients annually in the United States alone, the problem is widespread. Over this same time span, research has clearly documented persistent cognitive deficits following various cancer treatments, especially for the pediatric population, but there has been increasing investigation on the effects of systemic chemotherapy among adult cancer survivors. The nature of these findings will be summarized here to illustrate the rationale for cognitive and behavioral strategies that may help improve management of chemotherapy-related cognitive dysfunction. This chapter will describe a recently developed cognitive–behavioral treatment that is being studied to aid survivors with chemotherapy-related cognitive problems and outline future directions of management.

2.0. COGNITIVE EFFECTS OF CHEMOTHERAPY

Interest in the neuropsychological impact of cancer treatment dates back to the early 1980s when Silberfarb and colleagues observed measurable cognitive decline among patients undergoing cancer treatment.[3] However, many of these early studies had methodological shortcomings such as comparing chemotherapy recipients' neuropsychological performances to published norms and not matched control participants. Also, many studies evaluated chemotherapy recipients immediately following completion of chemotherapy regimes when acute effects of treatment, such as stress, anxiety, and depressive symptoms could adversely influence neuropsychological test performance. Nonetheless, these early results paved the way for more rigorous research that utilized control comparison designs and isolated the effects of anxiety, depression, fatigue, and menopausal status on cognitive performance.

In the mid-1990s Wieneke and Dienst[4] evaluated 28 women with a standardized battery an average of 6 months posttreatment with CAF (cyclophosphamide, doxyrubicin and 5-fluorouracil) and/or CMF (cyclophosphamide, methotrexate, and 5-fluorouracil). Seventy-five percent of patients scored greater than two standard deviations below published norms on one or more of the neuropsychological measures. Measures of working memory and sustained attention were most commonly affected. The pattern of cognitive impairment was unrelated to depression, type of chemotherapy, or time since treatment. van Dam *et al.*[5] then evaluated breast cancer patients an average of 2 years posttreatment who were randomized to high-dose chemotherapy plus tamoxifen or standard-dose therapy (FEC, 5-fluorouracil, epidoxorubicin, and cyclophosphamide) plus tamoxifen. They also included a control group of Stage I patients who were treated with local therapy only (surgery plus local radiotherapy). Patients in the high-dose arm were more likely to demonstrate cognitive impairment (37%). However, a greater number of patients in the standard-dose arm (17%) demonstrated cognitive impairment as compared to the local therapy group (9%). Stated another way, the risk of cognitive impairment was 3.5 times higher (95% CI $+$ 1.0$-$12.8) standard-dose patients versus local therapy patients. This finding suggested that cognitive changes may be dose dependent.

Schagen *et al.*[6] studied 39 breast cancer patients treated with CMF plus or minus tamoxifen and a control group of 34 age-matched axillary node negative breast cancer patients who received surgery and local radiotherapy but not systemic chemotherapy. Neuropsychological testing was approximately 2 years posttreatment. Results demonstrated patients treated with CMF had significantly more problems with concentration (31% versus 6%) and memory (21% versus 3%). Across all domains, cognitive impairment was seen in 28% of chemotherapy patients and 12% of controls. Comparison of chemotherapy patients who were ($N = 20$) and were not ($N = 19$) treated with tamoxifen showed no significant differences. Similar to those results, Brezden *et al.*[7] compared cognitive functioning in women with breast cancer who were currently receiving adjuvant chemotherapy (CMF or CEF, cyclophosphamide, epirubicin, and 5-fluorouracil) or were greater than 1 year post-chemotherapy (median, 25 months) to that of healthy controls. They found a greater number of patients in both groups had moderate or severe cognitive impairment compared to healthy controls.

In one of the more comprehensive studies to date, Ahles and Saykin, *et al.*[8] examined neuropsychological performance of long-term survivors (>5 years postdiagnosis, disease free) of breast cancer and lymphoma, that compared patients treated with systemic chemotherapy to those treated with local therapy. Analysis of the data demonstrated a significant multivariate effect across nine domains of neuropsychological functioning ($p < 0.04$) with survivors treated with systemic chemotherapy scoring significantly lower than survivors treated with local therapy only. Univariate analyses revealed significant treatment differences in the following domains: verbal memory ($p < 0.01$), and psychomotor processing speed ($p < 0.03$).

There was also a trend for spatial ability ($p < 0.10$) and visual memory ($p < 0.12$). Survivors who had received systemic chemotherapy scored lower than survivors who had received local therapy only. Using a definition of low neuropsychological performance similar to that used in the studies reported above, 39% of chemotherapy patients compared to 14% of local therapy patients scored within the low performance range (Chi sq. $p < 0.002$).

Overall these data support the hypothesis that a certain subset of cancer patients experience cognitive decline secondary to treatment with systemic chemotherapy. The functional domains affected generally appear to be verbal memory and psychomotor processing speed. However, the bulk of data show two distinct trends. First, not all cancer patients are equally affected. Ahles and Saykin, *et al.* found 24–50% of chemotherapy recipients had lower neuropsychological performance as compared to only 5–23% of survivors treated with local treatments in various neuropsychological performance domains. The result that not all chemotherapy recipients are found to have cognitive problems after treatment implies that some individuals may be more vulnerable than others to the cognitive effects of chemotherapy. Vulnerability factors, such as genetic predispositions (e.g., apolipoprotein, 4th allele), previous neurological insult, lower IQ, and lower "cognitive reserve" are all factors under investigation.[9,10] A second trend in the cognitive dysfunction and chemotherapy literature is neuropsychological performance scores of cancer patients who complain of memory problems after chemotherapy are usually normal-range. To date, there are few published longitudinal data examining pretreatment neuropsychological test performance to post-chemotherapy performance. It may be that those individuals who report problems in cognitive function after completing chemotherapy have had relatively high neuropsychological performance and thus their decline, although subtle, is more noticeable upon full resumption of functional activity such as employment or taking on full social or familial role responsibilities. In summary, an accurate picture of the etiological causes of cognitive dysfunction following chemotherapy remains elusive. In light of this fact, and given the growing number of patients undergoing chemotherapy and improved rates of long-term survivorship,[1,2,11,12] the application of existing nonpharmacological, behavioral, and cognitive compensatory strategies to this problem seems practical.[13–15]

3.0. OTHER FACTORS CONTRIBUTING TO NEUROPSYCHOLOGICAL PERFORMANCE IN CANCER SURVIVORS

As noted earlier, heightened levels of emotional distress and psychological symptoms can be associated with neuropsychological impairment. In addition, estrogen may play a role in the neuropsychological performance of cancer patients and survivors. Research on these effects is summarized below.

Depression. Numerous studies have shown neuropsychological deficits in depressed populations.[16–19] Most of this research has been conducted with participants who were experiencing a major depressive episode. Deficits found in this population include both short- and long-term memory deficits, as well as deficits in psychomotor function, new learning, and naming. For example, King *et al.*[20] found that, compared to age, education, and gender matched control participants who had no history of depression, depressed participants performed significantly worse on several neuropsychological tests, including word generation, verbal memory (both immediate and delayed recall), and visual memory (both immediate and delayed recall).

These findings are important because depressive symptoms are common among women diagnosed with breast cancer.[21] Since many of the neuropsychological symptoms of depression overlap with the neuropsychological effects of systemic treatments for breast cancer, it is important to take symptoms of depression into account.

Anxiety. Similarly, numerous studies have demonstrated neuropsychological deficits in individuals with anxiety disorders.[22–25] Most of these studies were conducted with participants who had been diagnosed with obsessive compulsive disorder (OCD), not simply people who suffered from anxiety. These studies have shown that individuals with OCD have weaknesses in visuospatial abilities and difficulty switching cognitive set. For example, in one study, patients with intractable OCD completed neuropsychological testing before undergoing psychosurgery and post surgery.[24] The participants were found to have deficits in information processing speed and visuospatial performance, as evidenced by performance on subtests of the Wechsler Adult Intelligence Scale-Revised Edition. These deficits were present before and after the surgery.

While it is important to note that this literature pertains most directly to individuals diagnosed with an anxiety disorder, most often OCD, less severe symptoms of anxiety may also play a role in neuropsychological performance. As many women with breast cancer suffer with some degree of anxiety,[26] it is important to consider the role of anxiety.

Fatigue. Most studies of the neuropsychological effects of fatigue have been conducted on participants diagnosed with chronic fatigue syndrome (CFS).[27,28] While some of these studies have identified deficits in attention, concentration, visuospatial abilities, and memory, others have found no differences between participants with CFS and normal controls.[29,30] Several researchers in this area have begun to differentiate between subjective cognitive effects and objective neuropsychological test performance.[31] While individuals diagnosed with CFS often report cognitive deficits, including a general slowing of information processing, they demonstrate relatively few, if any, deficits on neuropsychological tests.

It is important to note that these studies were conducted with participants who suffer from a specific disease, CFS, and not cancer treatment-induced fatigue which may have an etiology that is altogether distinct, such as compromised hemoglobin transport. Clinical intuition suggests fatigue probably does play a role in performance on neuropsychological tests, so it is important to account for it in this population, as many women undergoing treatment for breast cancer experience considerable fatigue throughout the course of their treatment and recovery.[32] In addition, episodic fatigue is a common complaint among cancer survivors following treatment. However, we are aware of no current data examining the effects of episodic fatigue on neuropsychological functioning among former chemotherapy recipients or other cancer survivors.

Sleep Disturbance. A recent review of the literature by Savard and colleagues found that between 31 and 54% of recently diagnosed and/or recently treated cancer patients reported sleep difficulties.[33] Even more startling was their finding that 23 –44% of cancer survivors continued to report significant symptoms of sleep disturbance up to 5 years posttreatment. In a sample of 300 women who had been treated with radiation therapy for nonmetastatic breast cancer, 51% endorsed some significant insomnia complaint, as determined by a report of current sleep difficulty or current use of sleep medications.[34] Overall, 19% of the total sample met the diagnostic criteria for insomnia, which represents almost twice the percentage of people in the general population who would meet these criteria.

Individuals with chronic insomnia often report decreased memory, attention, concentration, and motor performance.[35] A recent review of the literature on cognitive impairments in chronic insomnia concluded that, while results and methodology vary, there is objective evidence that chronic insomniacs demonstrate impairments in attention and vigilance.[35] Because chronic insomnia is prevalent in cancer patients and survivors, it is possible that sleep disturbance plays a role in their neuropsychological functioning.

Estrogen. In recent years, a great deal of research has been conducted on the effects of hormones, particularly estrogen, on cognition.[36–38] Like the neuropsychological research on fatigue, the research on the effects of estrogen provides mixed results, with some researchers finding that estrogen has an enhancing effect on neuropsychological test performance and other researchers finding no effect. However, methodological differences may explain these different findings. For example, researchers have used different estrogen preparations, have administered different neuropsychological tests, and none have measured actual estrogen levels.

Sherwin[39] assessed a group of premenopausal women before they underwent a surgical menopause and again 4 months post surgery. Half of the women received estrogen replacement therapy after the surgery, while the other half received a placebo. The women who received estrogen replacement therapy maintained their preoperative scores on all of the neuropsychological tests, while the placebo group demonstrated a significant decline in performance on verbal memory tasks. However, in a similar study, Ditkoff *et al.*[40] found no difference between an estrogen replacement group and a placebo control group. At this time, it is unclear what role estrogen plays in neuropsychological functioning following cancer treatment. The majority of breast cancer survivors are postmenopausal but many premenopausal women undergoing chemotherapy for cancer experience a chemically induced menopause. It remains unclear as to which of these women are vulnerable to neuropsychological decline following chemotherapy.

4.0. COGNITIVE REMEDIATION OF CHEMOTHERAPY-RELATED MEMORY DYSFUNCTION

Cognitive rehabilitation approaches have been generally shown to improve functioning of patients with subtle to severe cognitive deficits.[14,15,41] However, relatively little is known about rehabilitation of cognitive dysfunction among adult cancer survivors treated with systemic chemotherapy. For example, Cimprich[13]observed improvement in directed attention among stage I and II localized breast cancer patients who were treated with a brief attention restoration program—but participants in the study were patients who underwent surgery with no other cancer treatment. The cognitive remediation program (CRP) involved instructing patients to schedule daily relaxing activity in the natural environment—a procedure hypothesized to restore directed attention. Results suggested treated patients improved in directed attention performance but it is unknown if Cimprich's intervention would have similar positive results among past chemotherapy recipients. Further, the participants in the Cimprich study enrolled relatively soon after treatment (6 months) when recovery is expected to naturally occur. By contrast, many cancer survivors who report chemotherapy-related memory problems do so years following treatment.

Approaches to nonpharmacological cognitive remediation involve two broad types[41]: A traditional cognitive–rehabilitation approach that typically involves repetitive practice and drill in cognitive tasks to promote over-learning and aid circuitry repair and cortical reorganization.[15,42,43] Another approach is helping patients compensate for cognitive problems through use of behavioral and cognitive techniques (such as self-regulation and metacognitive training) to aid function in the environment.[42] This "compensatory strategy" approach is found in the pediatric behavioral medicine and neuropsychology literature. Specific strategies can include social skills training, audio-taping of lectures, teaching participants to make written outlines of reading material, using oral and written forms of tests, self-instructional training (SIT) and applied relaxation training.[44] Butler and Copeland[42] conducted a preliminary randomized, wait-list control trial with CRP that in essence combines the traditional cognitive rehabilitation and compensatory strategy approaches. Cognitive remediation program consisted of components similar to Attention Process Training (APT)[14] a multifaceted approach to enhance cognitive and behavioral function in specific areas of directed attention and distraction reduction. Twenty-one participants (mean age, 11.9 years, SD = 3.7) who were on average 4 years post-cancer treatment-treatment (SD = 3.7) enrolled in the CRP program. Compared to controls ($N = 10$), the CRP participants made significant gains in scores of sustained vigilance/attention (Continuous Performance Test), $p < .04$, and sentence memory, $p < .05$. Cognitive remediation program holds great promise for the population of pediatric cancer survivors. However, participants in the study had a variety of cancer treatments beyond chemotherapy (e.g., irradiation and surgical treatments) and six participants had central nervous system cancer, suggesting this intervention is best suited for developing pediatric cancer survivors who likely require intensive cognitive remediation and less suited for adult chemotherapy recipients. The concern about CRP is that it is a lengthy treatment consisting of up to 50 hours of training sessions. Adult chemotherapy recipients returning to vocational or social roles following treatment recovery may view the time commitment to CRP as too great. From that standpoint, a brief compensatory treatment approach may be helpful for the rehabilitation and readjustment to functional activity following cancer treatment.[45] Our group has developed a program with these aspects in mind.

5.0. COGNITIVE BEHAVIORAL MANAGEMENT

Memory and Attention Adaptation Training (MAAT) places an emphasis on learning strategies to compensate for subtle memory problems in daily life. This is a slight departure from a more traditional cognitive rehabilitation approach. Emphasis is placed on maximizing function and adaptation in the natural environment and not necessarily on cognitive restoration as measured by neuropsychological test performance.[15] In effect, MAAT presumes that the problem of chemotherapy-related memory dysfunction can be conceptualized from a "diathesis-stress" framework. That is, under times of low demand, such routine times at the workplace or household, cognitive dysfunction may not be a hindrance or cause undue interference. If problems of memory or attention arise, they are readily handled. By contrast, under times of high performance demand such as sales presentations, dispensing

Table 1. Outline of Memory and Attention Adaptation Training.

Visit	Content
1	• Treatment overview & provision of workbook • Education on memory and attention and effects of chemotherapy • Self-monitoring instruction • Relaxation training • Homework
Phone Contact 1	• Review Homework, problem solve
2	• Homework review • Compensatory strategy(ies) selection, instruction, and rehearsal • Homework
Phone Contact 2	• Review Homework, problem solve
3	• Homework review • Compensatory strategy selection, instruction, and rehearsal • Activity pacing and scheduling • Homework • Overview
Phone Contact 3	• Review Homework, problem solve
4	• Homework review • Compensatory strategy review • Activity pacing and scheduling review • Plan for relapse prevention • Wrap-up

dangerous medications, or socializing where simultaneous conversations occur, cognitive failures may become a greater hindrance to functional performance.

Specific techniques used in MAAT are drawn from the cognitive-behavior therapy (CBT) and rehabilitation literature related to an array of problem areas. These include: mild traumatic brain injury cerebral damage due to stroke or brain trauma and reading comprehension/attention.[15,46–49] Memory and Attention Adaptation Training is organized into four components: (1) education (on chemotherapy-related cognitive problems and other influences on attention and memory such as stress); (2) self-awareness training (self-monitoring to identify "at risk" situations or conditions associated with cognitive failure); (3) compensatory cognitive skills training; and (4) applied relaxation training for arousal reduction. Similar components have been demonstrated to aid patients with chronic symptoms associated with mild traumatic brain injury, stroke, and cancers of the central nervous system.[13,43,46–48]

The MAAT format could be characterized as falling on a spectrum of "guided self-help" in that the patient uses a workbook in conjunction with visits to the treating clinician. Memory and Attention Adaptation Training consists of four individual visits, once every 2–3 weeks, with three phone contacts (One between each visit) for support and review of procedures. This is a total of seven contacts. Visits are typically 50 minutes each. Participants also complete homework assignments or "applied exercises" between visits and thus telephone contacts serve as a venue to problem solving or address questions (see Table 1).

6.0. EVALUATION OF MAAT

Empirical investigation of MAAT efficacy is underway but far from complete. However, pilot research and preliminary data point to some support. In a single-arm feasibility study, 29 breast cancer survivors who were on average 8.2 years post-chemotherapy (SD = 4.4 years) completed the MAAT program. Principal outcome measures included self-reported cognitive function in daily life as assessed by The Multiple Ability Self-Report Questionnaire (MASQ)[50,51]; The Quality of Life Cancer Survivors scale, satisfaction ratings and a brief neuropsychological testing battery (the California Verbal Learning Test-II (CVLT-II)[52]; Logical Memory I and II from the Wechsler Memory Scale, 3^{rd} Edition[53]; Digit Symbol subtest from the Wechsler Adult Intelligence Scale III[54];Trail-making tests A & B[55]; Stroop Color-Word Interference Test.[56] Testing occurred at four time points: baseline, posttreatment, 2-month, and 6-month-follow-up. Participants were excluded if they had any history of neurological problems such as prior traumatic brain injury or central nervous system disease, substance history, epilepsy, or severe psychiatric illness. Results indicated a significant reduction in self-reported daily cognitive complaints as assessed by the MASQ, improved quality of life and high satisfaction ratings. Neuropsychological test score improvements were observed in tests of verbal memory (total score for the CVLT-II, Logical Memory Tests) and in processing speed. These neuropsychological test results, although positive, are interpreted with caution as there was no control group to rule out the effects of practice with repeated testing. Nonetheless, the pilot results did justify further investigation.

In a study being completed at the time of this writing, 26 breast cancer survivors at 18 months posttreatment were enrolled in randomized, wait-list control trial of MAAT. The mean age of participants was 50.7 years (SD = 6.2). The same exclusion criteria were used as in the previous study to rule out neurological or psychiatric influences on cognitive performance. Preliminary results were examined. Those individuals who were randomized to MAAT demonstrated reduced number of daily cognitive complaints relative to wait-list controls at posttreatment with adjustment to baseline differences in MASQ scores. Memory and Attention Adaptation Training participants also demonstrated some improvement in verbal memory as assessed by CVLT-II total score as compared to controls, and also provided high general satisfaction with treatment ratings. None of the results demonstrated statistical significance but the direction of trends suggest the MAAT participants improved in daily cognitive function and the approach continues to be modified to improve its impact, particularly given the absence of alternatives at this time.

Two other important points regarding the development and evaluation of MAAT need to be made. First, the approach the MAAT program takes is a practical and efficient delivery of existing methods to help individuals manage and cope with every day cognitive problems that can arise after a life-disrupting diagnostic and treatment process. It may be that self-efficacy in the mastery over cognitive symptoms in daily life is the key variable that MAAT targets and hence coping with, not *curing*, cognitive problems should be the principal aim of MAAT. Future research on MAAT should include self-efficacy in coping with cognitive problems as a dependent measure. A second point is related to using standardized neuropsychological tests as principal outcome measures. Current neuropsychological testing may not be sensitive to the subtle changes in daily cognitive function that many chemotherapy recipients report. While research cited earlier clearly shows differences in standardized neuropsychological test scores between groups of cancer survivors who do and do not undergo chemotherapy, these results show many cancer survivors who have cognitive complaints score in a normal range. Certainly, development of standardized tests of neuropsychological function in functional domains utilizing advance computer technology may help enhance identification of subtle changes in memory and attention function among affected cancer survivors. Development of such testing will be highly valuable to future cancer survivor research, such as that in the development of MAAT. In the case illustration to follow, these points are evident in the context of a breast cancer survivor who begins the process of adapting to life with cancer and long-term symptoms associated with treatment.

7.0. CASE VIGNETTE

The following case vignette illustrates the application of MAAT: Ms. A. is a 53-year-old university professor who was diagnosed with breast cancer with findings of a 2 cm tumor with 1 of 12 lymph nodes positive. Her tumor was low grade, estrogen and progesterone receptor positive. She had a lumpectomy and subsequently treated with four cycles of doxorubicin cyclophosphamide (AC) followed by radiation therapy to the breast. She then started hormone therapy with daily tamoxifen. She had taken an 8-week leave of absence from summer classes in her recovery from surgery and subsequent chemotherapy. She later resumed her position of instruction and writing at a reduced workload during her course of radiation treatments. While she experienced stress and fatigue during this time period she had no other complaints. Her family and social support network were regarded by her as satisfying and her economic needs were adequately met. After completing treatment she began to resume a full teaching load, committee work, and journal editing tasks that she had regularly completed prior to the onset of breast cancer.

When she began to resume full duties, Ms. A. began to notice she had word-finding difficulty during class lectures. She noticed that in the middle of explaining a technical concept, she would lose a word well-known to her and become frustrated and anxious, making the word-finding problem all the more difficult. She also began missing important meetings that she thought she had scheduled in her day planner and noticed that others would remind her of conversations she recently had for which she had no memory.

Ms. A. had inquired about the problem and was evaluated with a brief neuropsychological test battery. As seen in Table 2, her verbal memory performance as evaluated by the CVLT-II was in the normal-high range. She also completed tests of visual motor processing speed with similar findings of average scores. While

Table 2. Baseline and Posttreatment Neuropsychological and Self-Report Test Results of Ms. A.

Test	Pretreatment scores	Posttreatment scores	Normative comparison scores
MASQ Total Score (higher score, more cognitive failures)	120	93	81.25 (SD = 18.67)
CVLT-II Total Score (T-Score)	61	70	
Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-III (scaled score)	10	13	
Stroop Color-Word Test (in seconds; lower scores indicate better performance)	56	49.5	
CES-D (Depressive Symptoms; <16 normal range)	10	6	
State Anxiety T-score	47	40	

these neuropsychological tests demonstrated normal performance, it may have been slightly lower than expected given her estimated premorbid intellectual functioning (IQ equivalent score of 127). Her responses to the MASQ indicated the total score was 2.1 standard deviations above the mean of a sample of healthy women of comparable age (higher scores denote more cognitive complaints). Ms. A. did not report depressive or anxiety symptoms on standardized self-report measures that were in a clinical range, suggesting that depression or anxiety was not solely accountable for cognitive complaints.

MAAT Visit 1. Ms. A. began the MAAT program. In the first visit she was provided with a patient workbook and the background and educational highlights of cognitive effects of chemotherapy. An important point made during this time is showing patients data from the healthy control participants in previous research.[57] Essentially, everyday cognitive failures such as forgetting people's names, phone numbers, or where they placed belongings such as house keys are relatively common among healthy individuals. Interestingly, reported cognitive failures in these samples are similar in type to those reported by individuals following chemotherapy. The intent of pointing this out to affected cancer survivors is not to minimize or invalidate memory and attention problems following chemotherapy. Rather, the intent is to help cancer survivors recognize cognitive failures in daily life are common to all people and not every cognitive failure is attributable to chemotherapy. Other factors contributing to cognitive failure of daily life include stress, fatigue, environmental distractions, hunger, etc.—factors that are readily manageable and understood. While the effects of chemotherapy may be poorly understood, at least common factors that contribute to attention and memory failures can be addressed with behavioral strategies with relative ease. This is an important step in MAAT as it lays a therapeutic expectation of *management* of daily cognitive failures and not *elimination* of the problem—an impossible goal, given healthy control self-report data cited previously. This step also helps the participant in MAAT reduce distress-inducing attributions that could lay the cause of memory problems to factors that cannot be changed and thus spawn more feelings of helplessness. Therefore, a goal of MAAT is to prevent this helpless cycle and improve coping and self-management.

In the remainder of visit one, Ms. A. was instructed to self-monitor memory problems. She was instructed to fill out forms that identify environmental (e.g., noise), internal (e.g., fatigue, hunger), and affective (e.g., anxiety, stress) factors associated with memory failures that were judged by her as interfering. She was asked to complete forms on four to six experiences that exemplified problematic cognitive failures (journaling all cognitive failures would be impractical). Finally, Ms. A. was provided instruction in progressive muscle relaxation (PMR). The intent of PMR is to provide an arousal self-regulation strategy to help manage stress that can interfere with memory processes of recall and directed attention. Ms. A. completed the session with rehearsal of a 17-minute PMR exercise and was provided a CD for daily practice at home.

MAAT Phone Contact 1. Between visits 1 and 2 a scheduled 5-minute phone contact revealed a pattern where Ms. A. was experiencing anticipatory anxiety about word retrieval during class lectures. She also indicated difficulty following conversations at faculty meetings or when socializing with small groups of friends. A factor contributing to this was difficulty ignoring unimportant verbal content when several conversations co-occurred. She reported gradually avoiding these situations and was disappointed that she was withdrawing from valued relationships both at work and her social life. These situations were to be reviewed in visit 2.

MAAT Visit 2. In visit 2, time was spent reviewing PMR and self-monitoring of situations described above. With respect to PMR, an important question to ask is whether the participant has increased awareness or "mindfulness" of muscle tension in daily life. While daily rehearsal of PMR is important, the intent of the practice is to increase awareness and self-reduction of muscle tension in daily activity. Increased arousal and muscle tension is hypothesized to adversely affect cognitive processing such as recall or focused attention. Ms. A. reported that she got deeply relaxed during practice sessions and that she noticed her shoulders were tense during work hours. She was then coached in "quick relaxation" which is a method designed to help reduce muscle tension quickly to promote application of relaxation skills to everyday life. After this, Ms. A. again identified problems with following conversation in small groups. She noticed that she avoided going out with friends at regular gatherings. When she did socialize with her group of friends, she was withdrawn and quiet. She rated this as more important than her word-finding problems in class and out of concern it would adversely affect her friendships. Given this, a brief review of compensatory strategies in the MAAT manual was reviewed. It was decided that verbal rehearsal would be used in the form of attentive listening to one speaker, and clarifying what was said in an assertive but natural way—akin to an interviewer using reflection and clarification techniques to assure mutual understanding of what the interviewee is communicating. This was modeled and role-played in the visit with the clinician modeling the technique, then acting as the speaker. Ms. A. then left with the assignment of using the strategy in daily conversations as a means of practicing the strategy.

MAAT Phone Contact 2. In the second phone contact, Ms. A. noted that quick relaxation was a practical and efficient way for her to apply relaxation skills to everyday life. She noted she was less tense in daily conversation with others and in the classroom. She also indicated it helped her recall of words during lectures. This was surprising to her. Finally, she related that using verbal rehearsal and clarifying her communication with others lead her feel more at ease and she was enjoying her time socializing again. She attributed this to "going with the problem, not stopping it."

MAAT Visit 3. The third office visit of MAAT consisted of reviewing strategies to date and selecting another compensatory strategy. Ms. A. indicated that not only was she following conversations with ease she reported less difficulty with verbal recall in the classroom. Further, when she did happen to be "stuck" without a word mid-sentence, she reported she began to ask the class for the term or phrase she was struggling with in a "Socratic, academic fashion." In this way, she was increasing class participation at the same time she was managing her problems with word recall. The visit ended with a review of SIT,[58] which is a method to improve task attention and procedural memory. It involves "self-talk" or making overt the inner verbal dialogue one uses in completing tasks such as writing or any task involving discreet steps. She was also briefly instructed in activity scheduling, which was another stress management strategy drawn from both the Cimprich[13] study and depression treatment literature.[59] It simply involves scheduling a brief, pleasant activity each day to build in a positively reinforcing daily event that reduces the impact of tension and negative affect. The rationale for activity scheduling in MAAT is to provide another strategy that optimizes stress management and minimizes the effects of stress or negative affect on cognitive function.

MAAT Phone Contact 3 and Visit 4. In the last phone contact and final visit of MAAT, all strategies were reviewed. The phone contact focused on review of SIT and its application at the workplace. At visit 4 a maintenance plan was reviewed in detail

Table 3. Proposed Directions for Future Research

1. Longitudinal research (e.g., assessment of neuropsychological function before, during, and after cancer treatment) to determine the relative effects of chemotherapy on attention and memory performance.
2. Development of functional neuropsychological measures of memory and attention in daily tasks; perhaps making use of virtual reality technology to simulate "real world" memory and attention tasks. This may tap into subtle memory and attention failure that becomes more salient under conditions of increased demand for cancer survivors.
3. The role of APOE and other genetic markers in the long-term effects of chemotherapy on memory and attention function.
4. Continued evaluation of MAAT and other cognitive rehabilitation strategies for cancer survivors who have undergone chemotherapy or other cancer treatments.
5. Research on possible pharmacological or combined pharmacological and cognitive–behavioral strategies for management of cognitive dysfunction after chemotherapy.
6. The development and evaluation of possible "chemo-protective" agents to prevent chemotherapy-related cognitive problems.

as a means of helping Ms. A. maintain use of the strategies she has used to date, and to at least once per month review the manual to assure she is applying the strategies as planned. The maintenance plan was also explained as a way to build on skills learned and that the end of the brief treatment was only the "end of the beginning." In the future, new tasks or changes in social or vocational roles may require more or different memory functions and thus reviewing the manual on a regular basis was a means of always being prepared for new cognitive challenges that may arise. She was encouraged to call the clinic with questions.

8.0. SUMMARY

While much research remains to be completed on the cognitive effects of chemotherapy, it is hoped that this chapter has summarized knowledge to date and some future directions for treatment. To be sure, pharmacological interventions and chemo-protective agents may hold promise in preventing this widespread problem given the increasing numbers of individuals who undergo chemotherapy annually. More research on genetic and hormonal influences and their interaction with fatigue, anxiety, and depression are needed to discern their collective influence on function (see Table 3). Continued development and refinement of the MAAT program and similar strategies on many outcomes of importance to survivors (e.g., self-efficacy in self-management of daily cognitive problems, coping, vocational adjustment) is urged. It is hoped that this research will offer cancer patients and their families useful and practical methods to manage this is all too common problem that while subtle, can have significant impact on the survivor's function and overall quality of life.

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Chapter 17

Smoking Cessation and Cancer Survivors

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1.0. INTRODUCTION

In the past two decades, cancer has shifted from an acute disease with certain fatality to a curable or chronic condition with increasing rates of long-term survival. Due to advances in early detection and treatment, nearly 64% of the U.S. adults diagnosed with cancer will survive beyond 5 years compared to only 33% of individuals diagnosed in 1960.[1] With more than 10 million cancer survivors in the United States[2] and this number expected to double by 2050[3] there is a growing need to understand the unique medical, treatment, and psychosocial sequelae in this rapidly-changing population. Recognizing that cancer survivors are at increased risk for the development of second primary cancers, cancer recurrence, treatment late effects, and other chronic health conditions, there has been a call for multidisciplinary cancer care approaches to address behavioral risk factors that could reduce morbidity and mortality in cancer survivors.[4] However, despite this emphasis on the development of interventions to improve the post-diagnosis health of cancer survivors, tobacco use in cancer survivors is largely an underappreciated area for health behavior change.

While it is well-known that tobacco use is the leading cause of cancer mortality in the United States annually (30% or 80,000 of all cancer deaths),[5] continued smoking following cancer diagnosis also has adverse health outcomes. Specifically, cancer survivors who smoke have a higher risk of morbidity and mortality, treatment-related complications,[6–11] higher risk of recurrence and second primary disease,[7,12–19] and poorer quality of life.[20] In addition to well-established causal links to cancers of the lung and head and neck, smoking increases the risk of cancers of the pancreas, bladder, kidney, uterine cervix, stomach, and acute myeloid leukemia.[21]

Cancer survivorship provides extraordinary opportunities, as well as challenges to promoting smoking cessation.[22] By personalizing the harms of smoking and focusing efforts on the restoration and maintenance of good health, cancer diagnosis can be a catalyst for smoking cessation among cancer survivors and their tobacco-dependent loved ones. However, cancer also invokes unique challenges to smoking behavior change that must be considered in the development and implementation of smoking cessation programs for cancer survivors.

In this chapter, we will: (1) provide a rationale for the importance of providing smoking cessation programs to cancer survivors and their families; (2) review prevalence rates of smoking and cessation; (3) briefly review clinical practice guidelines for the delivery of evidence-based, smoking cessation interventions in cancer care; (4) summarize the unique challenges of promoting smoking cessation in cancer survivors, and (5) highlight future directions for promoting smoking cessation in cancer survivorship.

Cancer survivorship is a relatively new phase in the continuum of cancer care. Established by the National Cancer Institute (NCI) in 1996, the Office of Cancer Survivorship has adopted the National Coalition of Cancer Survivors (NCCS) definition of a cancer survivor[23] which specifies that "an individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends and caregivers are also impacted by the survivorship experience and are therefore included in this definition." Providing useful guideposts for cancer survivorship, Fitzhugh Mullan[24] outlined three seasons of survival each with unique sets of issues and concerns. *Acute survival* begins with the diagnosis of the cancer and is dominated by diagnostic and therapeutic efforts. *Extended survival* is a period during which a patient goes into remission or has terminated the active treatment and enters a phase of medical surveillance or "watchful waiting" with periodic examinations and tests. Psychologically, this phase of survival is often dominated by fear of recurrence and uncertainty. Patients may cope with physical symptoms such as fatigue and pain. *Permanent survival* is roughly equated with "cure"; however, medical late effects and psychosocial sequelae often persist as chronic reminders of cancer and its treatment. This review will focus predominantly on the extended and long-term phase of survivorship.

Because of the dearth of literature regarding other forms of tobacco use (e.g., cigars, pipes, smokeless tobacco), this chapter will focus on cigarette smoking. However, interested readers are referred to quality reviews on smokeless tobacco and other forms of tobacco.[25–27]

2.0. RATIONALE FOR PROMOTING SMOKING CESSATION AMONG CANCER SURVIVORS AND THEIR FAMILIES

While the general health risks of smoking are well documented, perhaps less disseminated are the specific health risks of continued smoking in cancer survivors and *specific benefits* associated with smoking cessation. As presented below, there is a growing body of literature supporting the positive effects of quitting smoking following cancer diagnosis. Smoking cessation among cancer survivors has been associated with a decreased risk of new primary disease, cancer recurrence and/or treatment complications. Although much of the prior work has been conducted with tobacco-related cancers, there is also evidence that cessation is associated with specific health benefits across non-tobacco-related cancer types as well. Cancer care providers are encouraged to provide personalized quitting advice about the health benefits of cessation as outlined in the following section so as to enhance quitting motivation in cancer survivors.

2.1. Survival

In head and neck, lung, and bladder cancer patients, smoking cessation has been associated with an increased length of survival following diagnosis.[8,11,28–30] Stevens[19] showed that head and neck cancer survivors who quit smoking during the first year after diagnosis had improved long-term survival benefits similar to those observed in never smokers. Cervical cancer patients who smoke during chemoradiation were found to have an increased risk of disease progression and mortality.[31] Furthermore, continued smoking in melanoma patients is known to promote the metastasis of malignant melanoma.[32]

2.2. Second Primary Cancers

In breast cancer patients, smoking cessation is associated with a lower risk of lung primaries and pulmonary metastasis[33] particularly for women treated with chest radiation.[34–37] Continued smoking in Hodgkin's disease patients has also been shown to increase the risk of lung primaries.[38] Multiple studies have demonstrated that head and neck cancer patients who quit smoking lower their risk of developing another new cancer, particularly in the lung, head and neck, gastrointestinal, and genitourinary regions.[12–14,17,39–41] Finally, smoking cessation in lung cancer patients decreases the risk of developing another lung tumor or other tobacco-related cancer, particularly head and neck or bladder cancer.[15,16,18,20,41]

2.3. Cancer Recurrence

Smoking cessation is associated with a lower risk of progression of bladder cancer[42,43] and lower chance of bladder cancer recurrence.[28,42,44] Stopping smoking is also shown to decrease the chance of recurrence in head and neck cancer patients..[17,19] It is well known that smoking cessation lowers the risk of other tobacco-related cancers, including uterine cervical, pancreatic, colon, and kidney cancers.[5,45,46]

2.4. Treatment Complications

Among head and neck cancer patients, smoking cessation has been associated with improvements in the effectiveness of radiotherapy and treatment response[9,20,29,47] and reduced symptoms of chemotherapy-toxicity (e.g., infection, cardiac, gastrointestinal, and respiratory problems).[35,48] Cessation in head and neck cancer patients may be the most important factor decreasing the risk of treatment complications from surgery and radiotherapy,[11,49] with patients who quit experiencing lower rates of oral mucositis and vocal hoarseness.[10,50–52] Relatedly, continued smoking in cervical cancer patients elevates the risk of major treatment complications from pelvic radiation, particularly gastrointestinal problems.[53] For presurgical patients, quitting smoking before surgery may decrease the risk of perioperative complications and complications from reconstruction, including deep venous thrombosis, poor wound healing, and pulmonary embolism.[54,55] In addition, the pharmacokinetic effects of nicotine alters the metabolism of medications such as beta-blockers, bronchodilators, analgesics, benzodiazepines, and phenothiazines, decreasing the efficacy and resulting in the potential need for higher dosages of medication.[56]

2.5. Quality of Life

Smoking cessation in the general population is associated with significant improvements in quality of life, including decreased physical symptoms, improved appetite, sleep quality, and energy, and improved emotional well-being[57] and continued smoking in cancer patients is also related to poorer quality of life.[58] Cancer patients and survivors who have quit smoking report greater self-esteem and perceived control and mastery, beliefs that are particularly valuable at a time when control over one's health is often reduced.

3.0. PREVALENCE RATES OF SMOKING AND CESSATION IN CANCER SURVIVORS

Despite the growing awareness of the risks of continued smoking and the health benefits of cessation, the prevalence of smoking in cancer survivors is surprisingly high and similar to the U.S. adult population. Population-based estimates from the 1998–2001 National Health Interview Survey (NHIS) data show that 20% of cancer survivors are current smokers[59] compared to 21% of adults in the general U.S. population.[60] Further, smoking rates in cancer survivors show significant age-specific, cancer-specific, and time since treatment trends. Younger cancer survivors (18–40 years old) are more likely to report current smoking (42.6%) compared to their age-matched cohort with no history of cancer (26.5%).[59] Also based on the 2000 NHIS data, Coups and Ostroff[61] reported that 37.7% of 18- to 39-year-old cancer survivors were current smokers compared to 26.2.% of non-cancer controls. Notably, time-stratified findings from Bellizzi *et al*[59] showed that smoking rates are highest in the first year from diagnosis (23.3%) but lower in the years following diagnosis (19.4%) and then slightly higher in longer-term cancer survivors ($\geq$10 years) (22.7%). Further, smoking rates are highest in gynecologic cancer survivors (37.3%) and survivors of lung and upper aerodigestive cancers combined (20.6%)[59] with the highest rates of smoking reported in cervical (46.0%) and uterine cancer survivors (29.4%).[61] Most prominent were findings showing that more than half of younger cervical cancer survivors (59.3%) report current smoking.[61]

Dramatic rates of smoking cessation have been observed in naturalistic and intervention studies with cancer survivors.[62–64] However, small clinic samples demonstrate much variability in these smoking cessation rates across cancer types and treatment modalities, suggesting that subgroups of survivors may be particularly vulnerable to continued smoking.[19,40,62,64–72] Initial and ongoing assessment of smoking status should be a routine part of follow-up care.

Recognizing the prevalence and risks of continued smoking in cancer survivors, many professional oncology organizations, including the Oncology Nursing Society,[73] the American Society of Clinical Oncology,[45] and the National Comprehensive Cancer Network[74] have issued consensus statements that support promoting smoking cessation in cancer care. Moreover, in recognition of the important role of smoking status on treatment response, and survival outcomes, it has been recommended that smoking status be routinely assessed and analyzed in all oncology clinical trials.[75]

4.0. CLINICAL PRACTICE GUIDELINES FOR THE DELIVERY OF SMOKING CESSATION INTERVENTIONS

Clinical practice guidelines have been developed for the delivery of brief advice and evidence-based smoking cessation interventions in health care settings.[76,77] Within cancer care settings, physicians, nurses and other cancer care providers can readily offer compelling advice to cancer survivors about the risks of continued smoking and the health benefits of quitting. Brief cessation counseling techniques known as the 5 A's model are widely recommended: (1) Ask about smoking, (2) Advise about quitting, (3) Assess readiness to quit, (4) Assist, and (5) Arrange follow-up.[78]

Clinical practice guidelines for treating tobacco dependence were first published in 1996 and then updated in 2000,[76] are based on an expert panel's comprehensive and systematic review of the evidence base for the management of tobacco-dependent patients. The eight key recommendations and findings are summarized in Table 1. Brief counseling involves assisting smokers to develop and use practical problem-solving and coping strategies for dealing with smoking urges, and to seek social support and encouragement from their social network.[76,78] The guidelines also highlight the efficacy of smoking cessation pharmacotherapies (i.e., Bupropion SR, nicotine gum, nicotine lozenge, nicotine inhaler, nicotine nasal spray, and nicotine patch) for all smokers attempting smoking cessation, except those with medical contraindications. These pharmacotherapies, several of which are now available over-the-counter, increase abstinence rates when compared to placebo.[76] Minimal or brief interventions for smoking cessation (e.g., lasting less than 3 minutes in duration) significantly increase tobacco abstinence rates, and higher intensity interventions (e.g., lasting over 10 minutes) are nearly twice as effective as brief advice. Multi-component cessation interventions in which health care providers deliver strong advice to quit with smoking cessation pharmacotherapy (e.g., nicotine replacement therapy), ongoing support and referral for more intensive cessation counseling can result in a twofold increase in quit rates.[76]

The 5-A's counseling model along with the clinical practice guidelines offer an evidence-based framework for promoting smoking cessation among cancer survivors and their families (Table 2).[76] Based on these well-established guidelines, several

Table 1. Clinical Practice Guidelines: Findings and Recommendations

- Tobacco dependence is a chronic condition that often requires repeated intervention.
- Effective tobacco-dependence treatments are available.
- Consistent identification, documentation, and treatment of every tobacco user in health care settings.
- Brief tobacco-dependence treatment is effective and should at least be offered to every smoker.
- Strong dose–response relationship between the intensity of tobacco- dependence intervention and effectiveness.
- Counseling and behavioral therapies are effective and should be used with all patients.
- Numerous pharmacotherapies for smoking cessation have proven efficacy and in the absence of contraindications should be used with all smokers attempting to quit.
- Tobacco-dependence treatments are cost-effective.

Source: Clinical Practice Guidelines, 2000.

Table 2. The "5 A's" for Brief Intervention

Ask about tobacco use.	Identify and document tobacco use status for every patient at every visit.
Advise to quit.	In a clear, strong, and personalized manner urge every tobacco user to quit.
Assess willingness to make a quit attempt.	Is the tobacco user willing to make a quit attempt at this time?
Assist in quit attempt.	For the patient willing to make a quit attempt, use counseling and pharmacotherapy to help him or her quit.
Arrange follow-up.	Schedule follow-up contact, preferably within the first week after the quit date.

Source: Clinical Practice Guidelines, 2000.

recent trials have examined the efficacy of promoting smoking cessation among cancer survivors.

4.1. Efficacy of Smoking Cessation Interventions in Cancer

Consistent with the clinical practice guidelines, these cessation interventions generally have included: standardized provider advice to quit, personalized education about the risks of smoking and the benefits of quitting, self-help print materials with content tailored to the needs and concerns of cancer patients, discussion and agreement on a quit date, and scheduled follow-up sessions. Interventions have been conducted in both outpatient and inpatient settings. The majority of studies have targeted lung and head and neck cancer patients.

Very few randomized smoking cessation clinical trials with cancer patients have been published. These studies have utilized small sample sizes, focused primarily on hospitalized patients, and used nonrandomized designs. Both minimal and more intensive programs have been associated with dramatically high rates of cessation suggesting that the cancer survivor population is quite responsive to these cessation programs.[63,79,80] In these studies, abstinence rates for the intervention (experimental) and usual care (control) conditions have been high, up to 70% in the first 6 months, far above the naturalistic quit rates reported in the general population of smokers (generally, 10% to 15%).[76] Gritz and colleagues[62,68] compared the effects of usual care (standardized physician advice including education about the risks of smoking and the benefits of abstinence) to intervention (standardized advice with three types of self-help materials tailored to the special needs and concerns of head and neck cancer patients, discussion about tobacco withdrawal, scheduled quit date, affirmation of continuing provider support, and six monthly booster sessions during outpatient follow-up). Gritz and colleagues[62] reported no significant intervention effect, however, 74% of the intervention arm and 77% of the usual care arm were biochemically verified to be abstinent. In this trial, significant positive predictors of cessation included surgical treatment (versus more intensive treatment), greater readiness to quit, less nicotine dependency, and being nonwhite. In a randomized trial, Wewers *et al.*[79] examined the effectiveness of a hospital-based intervention for 30 postoperative cancer patients (e.g., head and neck, breast, prostate, and cervical) consisting of three in-patient sessions followed by five post-discharge telephone calls. At 6 weeks, 64% of cancer patients in the intervention arm of this study quit compared to 50% in the usual care arm, although group differences were not statistically significant in this small clinic sample.[79] In a subsequent single arm study, Wewers and colleagues[80] conducted a hospital-based counseling intervention for 15 lung cancer patients. Follow-up results at 6 weeks indicated 93% of lung cancer patients reported a quit attempt, with 40% biochemically verified to be abstinent.[80] Schnoll and colleagues[81] randomized 432 cancer patients to a usual care (physician advice and standard cessation assistance) or intervention condition (physician-delivered brief advice for cessation; identification of a quit date; prescription for NRT; general self-help materials and referral to a national quit line, and follow-up assistance in subsequent visits). At 6-month follow-up, 11.9% of cancer patients in the usual care condition and 14.4% of cancer patients in the intervention condition quit, while at 12 months, 13% in the usual care condition and 13.3% in the intervention condition quit.[81] Significant positive predictors of smoking cessation included tumor site (e.g., having head and neck or lung cancer); smoking initiation before age 16; smoking more than 15 cigarettes daily, and greater desire to quit.[81] Two other published hospital-based smoking cessation studies in surgically-treated cancer patients have utilized small sample sizes ranging from 15 to 28, with 6-week smoking abstinence outcomes (ranging from 21% to 75% in the intervention arm and 14% to 43% in the usual care arm), and no treatment effects.[82,83] In addition, relapse rates following hospital discharge have been relatively high for both intervention and usual care conditions suggesting that the sustainability of these cessation efforts has not been fully addressed by current treatment approaches.[63] There is a need to examine the specific barriers associated with smoking cessation in cancer survivors and the efficacy of tailored cessation interventions.

5.0. CHALLENGES OF PROMOTING SMOKING CESSATION IN CANCER SURVIVORSHIP

Clinical practice guidelines predominantly based on the experiences of primary care patients may not fully accommodate the specific needs and considerations of cancer survivors and their families. Part of the challenge of tailoring smoking cessation interventions to meet the special needs of cancer survivors is that, at present, little is known about the naturalistic factors that impede their smoking cessation efforts.[84–87] Again, most studies understandably have focused on the treatment- and smoking-related characteristics of lung and head and neck cancer patients.[19,35,40,64,68–70,72] In the general population of smokers, multiple patient-, provider-, and system-related barriers (e.g., inadequate provider training to deliver cessation interventions, and inadequate access to cessation treatments) may impede the delivery of smoking cessation interventions and the effective dissemination of the clinical practice guidelines. The context of cancer diagnosis has unique impact on all of these barriers which are discussed below (Table 3).

5.1. Patient-Related Barriers to Smoking Cessation

There are several patient level barriers for smoking cessation in cancer survivors including high nicotine dependency, urgency of cessation advice, cancer-specific health beliefs, psychological distress, disease and treatment variables, social network influences and misreporting of smoking status.

Table 3. Smoking Cessation in Cancer Survivors

Benefits	Barriers
Improved survival rate	High psychological distress
Fewer treatment complications	High nicotine dependence
Improved treatment efficacy	Abrupt cessation vs. "commitment to abstinence"
Reduced risk of disease recurrence and 2nd primary tumor	Low quitting self-efficacy
Improved mastery and control	Knowledge deficits
Reduced risk of smoking-related chronic conditions	Negative social support

Patients diagnosed with tobacco-related cancers typically report long histories of heavy tobacco use.[62,68,86] Heavy cumulative tobacco exposure is associated with strong nicotine dependency and severe withdrawal symptoms (i.e., cravings, restlessness, difficulty concentrating, insomnia, etc.) following smoking abstinence. Thus, cessation approaches in cancer survivors may require consideration of combined pharmacotherapies to address both nicotine withdrawal and other common symptoms such as anxiety and depression.

The perceived urgency for abrupt and immediate cessation following cancer diagnosis may diminish the likelihood for long-term smoking abstinence. Smoking cessation programs often suggest the importance of behaviors such as preplanning a "quit date" and practicing techniques for coping with smoking urges. When cancer patients are hospitalized or otherwise immediately begin a course of active cancer treatment, this pre-quit planning phase may be necessarily disrupted. In addition, patients' pre-quit planning and problem-solving skills may be overwhelmed by psychological distress related to cancer diagnosis. We have found that smokers who are able to quit prior to hospital admission are more likely to maintain long-term smoking abstinence into extended survivorship. Thus, patients should be advised to give thoughtful consideration regarding how they can anticipate some of the quitting challenges, and elicit support.

Cancer patients may have a general lack of knowledge about the health benefits of smoking cessation specific to the course of their cancer. Indeed, tobacco-dependent cancer patients often report fatalistic health beliefs such as "the damage is done" and that "it is too late to quit." Compounded by an extensive history of heavy tobacco use, and the likelihood of prior failed attempts to quit smoking, self-doubting beliefs may foster low self-efficacy for quitting, a potent barrier to smoking cessation. Relatedly, cancer survivors' knowledge about specific health risks of smoking (e.g., impact on cancer recurrence or second primary cancer) may be potent motivators of smoking behavior change.[88] Wold and colleagues[88] examined causal attributions related to cancer diagnosis in cancer survivors and showed that most cancer survivors, regardless of smoking status, believed that smoking would cause the same type of cancer diagnosis in *other* people. However, only about 17% of former smokers and 30% of current smokers believed that smoking had caused their *own* cancer.[88] To address these health belief barriers, health care providers should offer personalized advice about the short-term benefits of smoking cessation when addressing patients' concerns about cancer risk factors, medical late effects and preventing disease recurrence. Further, targeted strategies to enhance quitting self-efficacy for demoralized patients may be highly effective given that cancer patients with higher self-efficacy for quitting are more likely to achieve and maintain long-term cessation.[84,89–94]

Stressful life events and negative affect (i.e., depression; anxiety, and anger) are well-known barriers to smoking cessation and strong triggers for smoking relapse following attempts to quit.[95] Heightened psychological distress has been reported along the entire continuum of cancer care in some survivors (e.g., ref. 96). Long-term and highly nicotine-dependent smokers may rely heavily on their smoking as a mood regulation strategy to decrease negative affect and increase positive affect.[95] Cancer survivors with high levels of negative affect or in particular, those survivors with comorbid anxiety, posttraumatic stress or depressive symptoms may be at acute risk for continued smoking or relapse. Indeed, by exacerbating illness, smoking itself is a stressor that the patient can take control over unlike other aspects of the cancer. Intensive cessation treatment for patients and survivors with high risk profiles for relapse (e.g., greater nicotine dependency, past or current depression) may have potential efficacy over brief treatments.

Disease and treatment variables may also influence smoking cessation. Patients with more advanced disease or those who receive more intensive treatments may have longer periods of hospitalization and enforced initial abstinence. Findings with hospitalized cancer patients indicate that smoking relapse is highest within the first month following hospital discharge.[68] It appears that as survivors recuperate, begin to regain feelings of normalcy, and resume social routines such as work and family roles, the urge to smoke may increase. Patients who undergo less aggressive treatment with less functional disability, may be exposed to more smoking cues and in turn, a greater risk of relapse. In studies examining predictors of continued tobacco use following cancer,[63,68]patients who are diagnosed with less severe or early stage, curable disease and those who undergo relatively less intensive treatment regimens are less likely to quit smoking. Patients with early stage disease who have a good prognosis for survival may minimize the magnitude of ongoing health threats. Treatment and disease-related sequelae in cancer survivors can also serve to undermine smoking cessation interventions in cancer survivors. Treatment late effects, such as xerostomia (dry mouth) or surgical resections affecting the oral mucosa may result in the inability to produce saliva and use smoking cessation medications, including the nicotine gum or lozenge. Further, patients with gastrointestinal (GI) sequelae may not be able to use the nicotine lozenge or gum as it may worsen GI symptoms. The tailoring of pharmacologic therapies for tobacco dependence and the need for newer approaches that address these problems in cancer survivors are indicated.

For cancer patients, initial abstinence often occurs in the context of a restricted hospital environment in which patients are isolated from family, friends and co-workers who smoke. Given that smoking is a behavior that clusters in families, due in part to family modeling, behavioral norms, and genetic propensities, the social networks of cancer survivors are likely to include other smokers. Following hospital discharge, the presence of household smokers and other peers who smoke may pose significant barriers for successful maintenance of abstinence for the long-term. Living with a family member who smokes means repeated exposure to smoking cues in the home environment as well as ready access to tobacco products. Evidence among patients with head and neck cancers suggest that the presence of other household smokers, most commonly a patient's spouse, is a significant predictor of smoking resumption.[63] Including family members in follow-up visits and taking time to encourage them to seek assistance for quitting is often necessary.

Cancer survivors may be reluctant to disclose their smoking status to health care providers or family members, a factor impeding the delivery and use of tobacco-dependence treatments. Much like pregnant smokers, cancer survivors may be reluctant to disclose their smoking status to their physicians due to fears of strong disapproval and criticism. Based on data from pregnant smokers documenting nondisclosure or under-reporting of quantity of smoking to health care providers,[97,98] cancer survivors may also perceive nonsmoking expectations from health care providers.[99] The usage of a structured question[100] which serially assesses patterns of smoking reduction before, during, and after cancer diagnosis may enhance the accuracy of disclosure of smoking status by survivors.

5.2. Provider-Related Barriers to Smoking Cessation

Inadequate staff training and provider attitudes may also deter the delivery of smoking cessation interventions. Despite the promulgation of the clinical practice guidelines, surveys report many primary health care providers feel unprepared to assist their patients in smoking cessation, and a majority of providers do not routinely advise or assist their patients in cessation attempts.[76,101–104] Findings estimate that smoking status is assessed in 50–66% of clinic visits,[103,105–107] and smoking cessation interventions are provided in 3–20% of smokers' visits.[107,108]

Within the cancer care setting, Sarna *et al.*[109] surveyed 4000 members of the Oncology Nursing Society (ONS) to assess cessation practice patterns and attitudinal and skill set barriers to the provision of cessation advice and assistance. The most frequently reported perceived barriers to the delivery of smoking cessation interventions by oncology nurses in this sample were: (1) lack of patient motivation, 74%; (2) lack of time, 52%; (3) lack of skills, 53%; (4) lack of knowledge about how to help patients quit, 40%; (5) lack of knowledge in general, 36%; (6) not wanting to add to patient's stress, 35%; (7) not wanting patients to feel guilty, 24%; (8) no difference due to poor prognosis, 23%; (9) lack of confidence in smoking cessation, 21%; and (10) lack of recognition/rewards, 16%.[109] These survey findings suggest that recognizing and addressing attitudes and competency toward the delivery of smoking cessation interventions are important areas for staff training.[109] Further, provider education to dispel myths and misconceptions about smoking cessation in cancer care is key. For instance, lack of patient motivation was identified by oncology nurses as a deterrent to providing cessation counseling,[109] yet national surveys indicate 70% of current smokers actually want to quit smoking.[110] Oncology patients report similarly high rates of quitting motivation. Further, brief smoking cessation interventions are effective (3 minutes or less to deliver), with effective training programs and strategies for enhancing provider skills in tobacco interventions increasing in availability, including certification programs, workshops, and academic detailing.[104]

5.3. Systems Level Barriers to Smoking Cessation

The removal of financial barriers for smokers in need of treatment for tobacco dependence is a public health priority in the United States, particularly for uninsured, underinsured, and underserved smokers. Although reimbursement for smoking cessation interventions is improving, there are limitations to the coverage of tobacco-dependence treatment, particularly intensive treatment. Less than 33% of employers provide coverage for smoking cessation interventions.[111] These services require expensive co-payments, limited coverage for face-to-face counseling (instead favoring less costly web-based or printed materials for self-help programs), and referral to public health programs that may not meet the specific needs of cancer survivors. However, there have been promising advances in recent reimbursement trends. Once solely affiliated with corporate wellness programs, smoking cessation treatment is now shifting toward consideration for inclusion as a medical benefit.[112] Further, based on data from 1997 to 2002, the percentage of health care plans that provide full benefits for pharmacotherapy has tripled. Tobacco-dependence treatment is now newly covered under Medicare Part B (2005), covering two cessation attempts annually and a maximum of four intermediate sessions (3–10 minutes) or intensive sessions (>10 minutes) each time with a maximum of eight sessions annually. Of clear relevance to cancer survivors, eligible beneficiaries include smokers with a health condition linked to tobacco use.

In addition, the lack of universal screening for patients' smoking status represents another important systems-based gap and barrier to smoking cessation service delivery. A screening model would include documentation of the patient's smoking status, tobacco history, whether smoking cessation assistance was provided, as well as electronic referral to a smoking cessation program. The follow-up and tracking of program participants and their progress allows for the monitoring of smoking cessation outcomes and service delivery. These system enhancements, which include staff education and clinic reminders, have been shown to be effective in disseminating cessation treatment and assistance in primary care settings.[113]

6.0. CLINICAL CARE APPROACHES FOR PROMOTING SMOKING CESSATION IN CANCER SURVIVORSHIP

A variety of approaches and models have guided the delivery of smoking interventions in health care settings. Tobacco interventions have involved stepped-care strategies, treatment matching strategies, and tailored intervention strategies. Stepped-care approaches range from minimal contact, self-help interventions to intensive counseling interventions by formal treatment programs. Stepped-care approaches are cost-effective public health models developed to maximize the reach of efficacious tobacco treatments among the general population.[114–117] The goal of stepped-care methods is to refer treatment failures to increasingly more intense treatments in response to demonstrated need.[76,116]

Our smoking cessation program at Memorial Sloan-Kettering Cancer Center follows a stepped-care model (see Figure 1), with all cancer care providers able to provide "step 1," minimum intensity counseling to patients. "Step 2" includes moderate intensity counseling through referral to the smoking cessation program, in which certified Tobacco Treatment Specialists (TTSs) (nurse specialists) perform an intake assessment of smoking behaviors, develop a tobacco treatment plan, offer brief counseling for cessation, advise options for smoking cessation pharmacotherapy, and conduct serial follow-up assessments with patients and survivors to monitor smoking cessation status and outcomes. Recognizing the geographic range of cancer survivors treated at a tertiary cancer care center, the TTSs also refer to local resources in the community. "Step 3" is intensive treatment for smoking cessation delivered by psychologists who provide specialized care of smokers at high risk for continued smoking in individual counseling sessions. In the more intensive intervention delivery model, we recognize and fully integrate the unique psychosocial needs of tobacco-dependent cancer survivors (e.g., psychological distress; treatment side-effects, and functional disability).

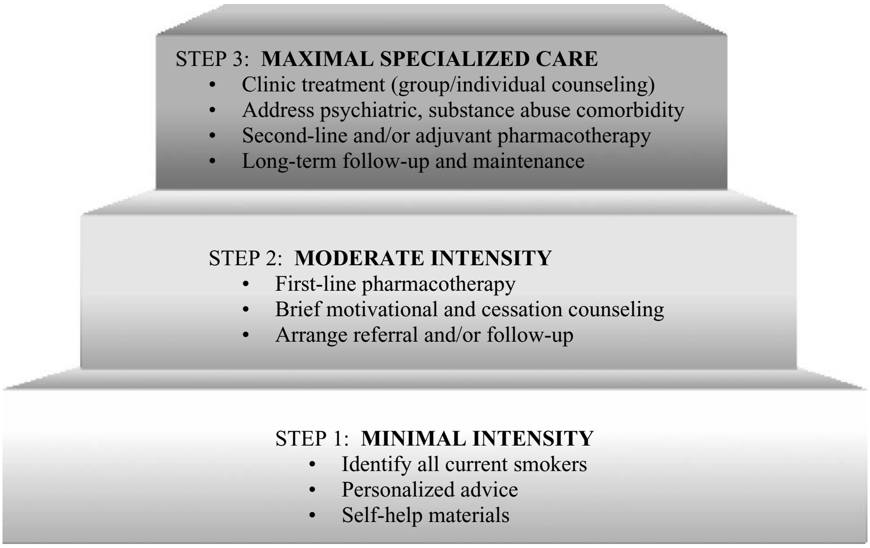

Figure 1. Memorial Sloan Kettering Cancer Center Smoking Cessation Program Stepped-Care Model.

A variety of long-term follow-up care approaches for delivering health care across the cancer continuum have evolved, including shared-care models (e.g., integration of oncology care with primary care follow-up), nurse-led models, and specialized multidisciplinary survivorship follow-up care clinics.[118,119] These public health approaches are intended to reduce cancer-related morbidity in cancer survivors. At present, national guidelines for the provision and coordination of care for cancer survivors including screening and surveillance; treatment of medical late effects, symptom management; genetic counseling and smoking cessation counseling are still in development.[118] Although formal measures to ensure the delivery of quality health care in survivors have not yet been universally adopted, the readiness and capacity of oncology specialists and primary care providers to offer long-term follow-up is being increasingly expected. National surveys show that nearly one third of all cancer-related visits made to physicians in 2001 to 2002 were made to primary care physicians.[118] When long-term survival is achieved, the “transition” of survivorship care “from oncology to primary care” (p. 2461; ref. 119) necessitates that health care providers manage the medical and health promotion needs of cancer survivors with a variety of disease and treatment late effects and surveillance needs.[119] As such, the challenge for health care providers and health systems is to identify the combination of health services, information systems, and survivor needs to improve health outcomes. Of the specific measures proposed to reduce cancer-related morbidity in survivors, screening for tobacco dependence is essential, and the delivery of minimal and intensive cessation interventions must be integrated into the comprehensive care of survivors in primary care follow-up and community oncology clinics.

Long-term follow-up visits and ongoing cancer surveillance provides numerous opportunities for promoting smoking cessation to cancer survivors and their tobacco-dependent family members. Providers’ efforts to promote cessation should be salient to the unique opportunities and challenges of points in the transition of cancer care. Ready availability and concurrent provision of self-help guides, pharmacologic assistance, and scheduled follow-up consistent with the clinical practice guidelines is critical. Evidence-based self-help cessation guides, group programs sponsored by national organizations such as the National Tobacco Quitline (1-800-784-8669; www.smokefree.gov) and an ever-growing armamentarium of pharmacotherapies are widely available to providers to support their efforts. For tobacco-dependent survivors with comorbid psychological distress, referral to specialized providers, including those identified by the American Psychosocial Oncology Society (http://www.apos-society.org/) and other cancer care organizations may be warranted. The dissemination of best practices for long-term follow-up in cancer survivors will include the tailoring of cessation interventions for this growing population.

In keeping with our efforts at MSKCC to promote smoking cessation among tobacco-dependent cancer patients, we have observed that cancer survivors' motivation for smoking cessation is enhanced by having greater personalized knowledge of the health benefits of cessation by cancer site and treatment modality. As part of our smoking cessation program, we have developed and published a self-help booklet ("Smoking Cessation Guide for Cancer Patients and Their Families")[1] tailored to the unique needs of cancer patients. We have also created several patient bookmarks highlighting the specific benefits of smoking cessation for subtypes of cancer patients. These educational materials have raised awareness among providers and patients. Program evaluation related to treatment delivery and smoking cessation outcomes, as well as the long-term cost-effectiveness is currently ongoing.

7.0. FUTURE DIRECTIONS FOR PROMOTING SMOKING CESSATION IN CANCER SURVIVORSHIP

Recognizing the high rates of cessation in cancer patients and the persistent risk for smoking resumption in survivorship, there is a need to develop and evaluate cessation treatment interventions that promote long-term smoking abstinence among cancer survivors. Emerging findings from longitudinal studies using both quantitative and qualitative methodologies to identify barriers and facilitators of smoking abstinence will help guide the tailoring of optimal pharmacological and behavioral interventions.

At an individual treatment level, there is first a need to target and examine the effectiveness of established evidence-based treatments for tobacco dependence in cancer survivors. Interventions developed for the general population of smokers may be applicable to the cancer survivor population.[22] For instance, Schnoll and colleagues, recognizing the potential barrier of psychological distress, are conducting a randomized clinical trial examining whether combination pharmacotherapy including bupropion (in addition to NRT and behavioral counseling) increases quit rates in head and neck cancer patients over and above NRT and behavioral counseling alone. Presumably, the more intensive treatment condition (addition of bupropion) will be superior and more responsive to the psychological needs of cancer survivors, many of whom report heightened psychological distress. These important findings will replicate work conducted in the general smoking population and may support treatment matching approaches for cessation interventions that are tailored to the psychological needs of cancer patients and survivors.

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[1] These patient education materials are available from the authors by request.

In addition to examining the application of pharmacological treatments for cancer survivors, there is a need to enhance behavioral interventions to promote long-term smoking abstinence. For instance, based on learning theory, scheduled reduced smoking (SRS) involves a progressive and systematic reduction in smoking rate by lengthening the duration of time between cigarette consumption.[120]By adhering to a discrete tapering schedule, delivered using a handheld computer, smokers can develop coping strategies in response to an increasing delay between cigarettes, relying less on smoking itself as a coping strategy.[121] We are currently testing the efficacy of an SRS behavioral intervention for newly-diagnosed cancer patients scheduled for surgery with follow-up assessments conducted into the extended phase of survivorship. We hypothesize that presurgical SRS will enhance quitting self-efficacy leading to improved maintenance of smoking cessation in hospitalized cancer patients. Additional research and clinical efforts in this direction seem warranted.

Further, emerging research is examining the pharmacologic, genetic, and behavioral determinants of smoking cessation and deciphering the complex nature of nicotine dependence. Findings from multidisciplinary studies will likely improve the understanding of smoking behavior change and maintenance in cancer survivors, and advance potential interventions for smoking cessation and disease prevention in this increasing population. For instance, Lerman and colleagues.[122] are investigating genetic variation in treatment response to smoking cessation pharmacotherapies. Future knowledge about genetic variation in the propensity for tobacco dependency and treatment response may aid targeted interventions in survivors of specific cancer types, such as lung cancer.[22,122]

From a health systems level, screening for smoking status and cessation assistance should be routinely offered in the long-term follow-up care of survivors.[118] For patients and survivors who are recent quitters, Gritz and colleagues[22] have also recommended provider consideration of biochemical verification (e.g., alveolar carbon monoxide ratings) of smoking status so as to facilitate frank discussion of individual barriers to cessation. Referral for more intensive cessation care that takes into account the unique needs of cancer survivors may be indicated. While survivors of tobacco-related cancers may be more likely to receive education and assistance for cessation, survivors of all cancers should be encouraged to quit and be made aware of the health-specific benefits of cessation for all cancer types.

Finally, given the challenges of reaching pediatric cancer survivors many of whom may be geographically dispersed and have varied contact with their pediatric cancer care providers, Emmons and colleagues are evaluating the effectiveness of disseminating a multicomponent behavioral and pharmacological cessation treatment using a web-based delivery model. Results from this ongoing clinical trial will guide the development of standards of care for the widespread delivery of smoking cessation services for pediatric and adult survivors in community as well as tertiary cancer care settings.

8.0. SUMMARY

Strong and consistent epidemiological evidence attests to the potential benefits of smoking cessation on cancer treatment outcomes, survival, prevention of recurrence and development of second cancers and chronic diseases. Cancer survivorship represents a critical opportunity for health promotion intervention related to smoking behavior change.[75] Evidence suggests that there are dramatic rates of smoking cessation for most survivors (e.g., 70%). However, there are subgroups of cancer survivors with high rates of continued smoking or risk factors for relapse, suggesting that innovative cessation approaches must be developed and evaluated. Cancer care providers are well positioned to address the many challenges faced by survivors. At present, in the United States, both the American Society of Clinical Oncology and the Oncology Nursing Society support the promotion of smoking cessation in cancer care settings and urge oncology practitioners to advise and assist in smoking cessation efforts. However, there are many patient, provider and systems level challenges unique to the cancer context in operation that present barriers to the delivery, uptake, and long-term effectiveness of smoking cessation interventions for the growing cancer survivor population. Addressing these barriers now is essential.

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Chapter 18

Psychological Distress, Depression, and Anxiety

Arthur M. Nezu and Christine Maguth Nezu

1.0. INTRODUCTION

This chapter focuses on psychosocial interventions geared to address the serious problems of stress, depression, and anxiety related to the experience of cancer and its treatment. Based on the authors' research and clinical work in psychosocial oncology, there will be an emphasis on problem-solving therapy approaches to secondary prevention interventions.

2.0. STATEMENT OF THE PROBLEM

Considerable medical progress has been made in treating the set of diseases known as cancer. Many forms are curable and there is a sustained decline in the overall death rate from cancer when one focuses on the impact on the total population.[1] Because of improvements in medical science, however, more people are living with cancer than ever before. Although the extensive medical needs of such patients may be well attended to, psychosocial and emotional needs are often overlooked.[2] Almost every aspect of one's life can be affected, as cancer engenders many stressors and can lead to significantly compromised quality of life.[3] Even for people who historically have coped well with major negative life events, cancer and its treatment greatly increases the stressful nature of even routine daily tasks. Weisman and Worden decades ago first referred to this situation for cancer patients as an "existential plight," where one's very existence may be endangered.[4] Recognizably, not every individual diagnosed with cancer will experience a plethora of problems, but most patients do report significant difficulties.

2.1. Prevalence of Psychiatric Disorders

Estimates of the prevalence of psychological difficulties range between 23% and 66% across cancer populations.[5] For example, in a study of 215 cancer patients with mixed diagnoses, 53% were found to be adjusting normally to stress; however, nearly half (47%) had clinically apparent psychiatric disorders.[6] Of these individuals, over two thirds (68%) had reactive anxiety and depression (adjustment disorders with depressed or anxious mood), 13% had major depression, 8% had an organic mental disorder, 7% had personality disorders, and 4% had anxiety disorders. In addition, of the psychiatric disorders observed in this population, 90% were reactions to, or manifestations of, the disease or treatment itself.

In a more recent study, among a sample of adults diagnosed with first onset head and neck or lung malignancies, the 12-month incidence of posttraumatic stress disorder was found to be 14%, 20% for other anxiety disorders, and 20% for depressive disorders.[7] Okamura *et al.* found that among a sample of women who experienced a first recurrence of breast cancer, 42% met diagnostic criteria for major depressive or adjustment disorder.[8]

2.2. Depression

Depression is a common experience among cancer patients. Studies utilizing both self-report and clinical observations suggest that major depression affects approximately 25% of cancer patients.[9] It is also responsible for the largest percentage of psychiatric consultations for cancer patients. For example, Massie and Holland found that among 546 patients referred for consultation due to emotional distress, 54% had diagnoses of adjustment disorder with depressed mood and another 9% had diagnoses of major depressive disorder.[10] Another study found a fourfold increase in the rate of depression among oncology patients as compared to the general population, underscoring the seriousness of the problem.[11]

Factors associated with greater prevalence of depression include a higher level of physical disability, advanced disease stage, and the presence of pain.[12] Also, higher rates of depression have been associated with the side effects of medications and treatment for cancer. Chemotherapy and oncological surgical procedures are a source of possible iatrogenically-induced depression in cancer patients because of their negative side effects that may include body image disturbances and physical symptoms.[13] For example, it has been estimated that 40% to 60% of patients' emotional distress is directly attributable to the cancer treatment itself.[14]

Numerous studies have also investigated various psychosocial risk factors for developing depression among cancer patients. Some of these risks identified include premorbid coping skills, social isolation, first degree relatives with a history of cancer and depression, a personal history of depression, a personal history of alcohol or other substance abuse, and socioeconomic pressures.[13]

2.3. Anxiety

Oncology patients often experience anxiety, for example, while waiting to hear their diagnosis, before procedures, treatment and diagnostic tests, and while waiting for test results.[15] In addition, cancer treatments themselves can be anxiety provoking and may contribute to the actual psychological morbidity of patients with cancer.[16]Studies indicate that anxiety can increase during certain periods of the disease, such as the discovery of the tumor, then peaks during surgery and remains high until a year subsequent when it begins to decline.[15] For some patients, anxiety can become so severe that they may be unable to adhere adequately to their medical treatment and seek to avoid fear-provoking procedures.[17]

Anxiety disorders appear to be more common in persons with cancer than controls or other chronic illnesses in the general population. Maguire *et al.*, for example, found moderate to severe anxiety in 27% of a sample of breast cancer patients as compared to 14% in a control sample.[18] In addition, Brandenberg *et al.* identified 28% of advanced melanoma patients as having anxiety compared to 15% of familial melanoma patients with no diseases.[19] Massie and Holland reported that anxiety accounted for 16% of requests for psychiatric consultations among inpatients.[10]

Some researchers have suggested that cancer survivors may respond to the psychological distress and uncertainty about the future by displaying posttraumatic stress disorder (PTSD)-like symptoms similar to those experienced by victims of war or environmental disasters.[20] Some of these symptoms have been reported as somatic vigilance and recurrent recollection of illness-related events, as well as symptomatology around anniversary dates. However, these symptoms appear to dissipate over time as the fear of recurrence lessens. Other studies have reported symptoms characteristic of stress or trauma symptoms in survivors of cancer, such as avoidant behaviors, intrusive thoughts, and heightened arousability.[21]

3.0. PSYCHOSOCIAL INTERVENTIONS FOR CANCER PATIENTS

Given the above description documenting the negative psychosocial consequences of cancer, the importance of developing effective interventions to improve the quality of life of cancer patients appears obvious.[22,23] In fact, Redd[24] suggests that an important factor responsible in part for the birth of psychosocial oncology as a field was the publishing of certain studies that underscored the successful use of behavioral procedures to control the anticipatory side effects of cancer chemotherapy, such as nausea and vomiting.[25] Moreover, during the past two decades, a sufficiently large number of intervention studies have been conducted engendering a number of qualitative and quantitative review articles.[26–29] The general conclusion that the majority of these reviews reached underscores the efficacy of a wide variety of psychosocial interventions geared to improve the quality of life of adult cancer patients. For example, Meyer and Mark conducted a meta-analysis of 62 treatment-control comparisons and found the beneficial and significant effect size *d*s were .24 for emotional adjustment measures, .19 for functional adjustment measures, .26 for measures of treatment-and disease-related symptoms, and .28 for compound and global measures.[29] However, similar to a qualitative literature review regarding earlier published studies,[30] significant differences among varying types of treatment approaches (e.g., behavioral versus supportive group therapy) were not found.

Because a comprehensive review of the treatment outcome literature for cancer patients is beyond the scope of this chapter, the reader is directed to the listed review articles (see also Baum and Andersen[31]). However, we should briefly note that such interventions can be grouped into the following general categories: educational interventions, cognitive–behavioral strategies, and group therapy approaches.

3.1. Educational Interventions

The major goal of educational strategies is to reduce cancer patients' distress and improve their sense of control that may be engendered by lack of knowledge and feelings of uncertainty. The topics covered include technical aspects of the disease and its treatment, potential side effects, navigating the medical system, and the physician-patient relationship. Research suggests that providing such information can lead to beneficial effects, such as decreases in depression and anxiety.[23]

3.2. Cognitive–Behavioral Interventions

Cognitive–behavior therapy (CBT) embraces an empirical foundation that focuses on the inter-relationships among behavior, thoughts, emotions, and biological events regarding mental health problems and medical symptom development and persistence. CBT, in this context, incorporates a wide array of intervention strategies that attempt to change those behavioral, cognitive, and affective variables that mediate the negative effects of cancer and its treatment. Many strategies under the CBT umbrella are theoretically based on principles of respondent and operant conditioning, such as contingency management (e.g., changing the consequences of behavior to change the behavior), biofeedback, relaxation training, and systematic desensitization, whereas other strategies are more cognitive in nature and include techniques such as cognitive distraction, cognitive restructuring, guided imagery, and problem-solving training. Applications of CBT for cancer patients have addressed both specific negative symptoms (e.g., anticipatory nausea, pain), as well as overall distress and quality of life.

3.3. Supportive Group Therapy Approaches

The potential strengths of group psychotherapy for cancer patients are threefold: (a) it can provide for a milieu in which people with similar experiences can provide emotional support to each other; (b) it is cost-effective for the patient; and (c) it is time-efficient for the mental health professional. One cautionary note—research suggests that group therapy programs which focus primarily on providing peer support and emphasize the shared expression of emotions are less effective than either educational protocols or programs that teach coping skills.[32]

4.0. OUR CONTRIBUTIONS TO SECONDARY PREVENTION OF PSYCHOLOGICAL DISTRESS—THE ROLE OF PROBLEM SOLVING AND PROBLEM SOLVING THERAPY (PST)

Problem solving in real-life situations, often referred to as "social problem solving," is considered to be an important psychological variable that mediates the impact of cancer.[23] In this context, it is defined as "a general coping approach that can help people manage or adapt to any stressful situation, thereby enhancing their flexibility and perceived control and minimizing their emotional distress even in situations that cannot be changed for the better" (p.10).[33] Therefore training individuals under stress in various problem-solving skills is hypothesized to lead to improved quality of life and decreased emotional distress. Such a hypothesis has been found to be valid across a wide range of patient populations, ages, and psychological difficulties.[34]

The conceptual relevance of problem-solving therapy (PST) for persons with cancer in particular is embedded in a general problem-solving model of stress, whereby the experience of cancer is conceptualized both as a major negative life event and the cause of a series of stressful daily problems.[35] Both sources of stress are further hypothesized to increase the likelihood that a cancer patient will experience significant psychological distress, such as depression and anxiety. However, one's problem-solving ability is conceptualized as an important moderator of these relationships, whereby effective problem-solving ability should attenuate the probability of experiencing distress, even when the person is confronted by cancer-related difficulties.

The core assumptions of this model have been supported by research findings regarding both university students and clinical patient samples,[36–45] as well as among adult cancer patients.[36,37] For example, in one study that focused on a group of 105 patients who recently had been diagnosed with cancer, we found that study participants who were characterized by less effective problem solving also reported higher levels of anxiety and depressive symptomatology, as well as greater numbers of cancer-related problems.[36]

In a second study, we attempted to assess the predictive relationship of problem solving to cancer-related distress among a sample of 64 women who had successfully undergone surgery for breast cancer from one to 13+ years prior to their participation in the investigation. Results indicated that problem solving was found to be a significant predictor of psychological distress, whereas time since surgery was not associated with cancer-related distress symptomatology.[36] In a further study, we identified the following relationships—under *similarly high levels of cancer-related stress,* those patients who were characterized as *ineffective* problem solvers reported *higher* levels of depression as compared to their cancer patient counterparts who were characterized as *effective* problem solvers.[37]

The major implication of this model for treatment, then, suggests that providing PST to patients with cancer should increase their ability to cope more effectively, and therefore, should impact positively on their distress and quality of life. This is in keeping with Andersen's (2001) biobehavioral model of cancer stress and disease course, which in part underscores the importance of impacting on a cancer patient's level of stress as a means of enhancing his or her quality of life and potentially improving the overall disease outcome.[46] Previous research that has identified PST to be an efficacious clinical intervention for a variety of psychological disorders,[47,48] especially major depression,[49–51] offers additional support for the hypothesis that PST would be an efficacious intervention for such goals among adult cancer patients.

4.1. Project Genesis: PST for Distressed Adult Cancer Patients

Given the above context, we conducted a 5-year randomized clinical trial entitled Project Genesis to assess the efficacy of PST as a means of improving the quality of life of distressed adult cancer patients.[52] In this clinical trial, adult cancer patients who were experiencing significant distress and depression were randomly assigned to one of three conditions: (a) ten 1.5-hour sessions of individual PST; (b) ten 1.5-hour sessions of PST provided simultaneously to both the cancer patient and his or her designated significant other (e.g., spouse, family member); or (c) a "treatment as usual" control. The condition that involved a significant other was included to assess the enhanced effects of formalizing a social support system where the role of the significant other was conceptualized as a "problem-solving coach."

Table 1. Specific Training Activities Associated with Four Rational Problem-Solving Tasks

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Problem Definition and Formulation

- Gather all available facts about the problem
- Describe these facts in clear and unambiguous terms
- Differentiate between facts and assumptions
- Identify those factors that make the situation a problem
- Set realistic problem-solving goals

Generation of Alternatives

- Generate a comprehensive list of alternative solutions
- Defer critical judgment
- Think of general strategies, as well as tactics for each strategy, when generating possible solution ideas

Decision Making

- Evaluate each alternative by rating (a) the likelihood that the alternative, if implemented optimally, will achieve the desired goals, and (b) the value of the alternative in terms of personal, social, long-term, and short-term consequences
- Choose the alternative(s) that have the highest utility

Solution Implementation and Verification

- Carry out the chosen plan
- Monitor the effects of the implemented solution
- Compare or match the predicted and actual effects
- Self-reinforce if the match is satisfactory: recycle through the process if the match is unsatisfactory

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PST in this study was based on the empirically validated problem-solving training manual originally developed for major depressive disorder[53] and revised specifically for an adult cancer population.[33] The overarching goals of PST are to improve an individual's overall problem orientation and rational problem-solving skills, while inhibiting tendencies to be impulsive or avoidant. Training in *problem orientation* is geared toward providing patients with a rational, positive, and constructive set or cognitive appraisal to problems in living and problem solving as a means of coping with them. The specific therapy objective is to change those attitudes or beliefs that inhibit or interfere with attempts to adaptively cope with stressful problems. In addition, participants are taught (a) to label emotions as cues as a means of identifying the existence of a problem, and (b) to inhibit the tendency to respond automatically in either an impulsive or avoidant manner, but rather, to engage in a systematic and planful style of problem solving.

Training in *rational problem-solving* involves teaching patients to (a) better define and formulate the nature of problems, (b) generate a wide range of alternative solutions, (c) systematically evaluate the potential consequences of a solution and select the most optimal ones to implement, and (d) monitor and evaluate the actual solution outcome after its implementation (see Table 1 for a list of specific training activities). In Project Genesis, Session 1 of ten sessions involved a general introduction to the program, whereas Sessions 2 and 3 were devoted specifically to the problem-orientation component, and Sessions 4–6 involved didactics and practice in the four rational problem-solving skills. The last four sessions provided for an applied integration of the model, as well as continued practice in the various problem-solving components. Emphasis on the problem-orientation component continued throughout treatment. In addition, between-session homework assignments, relevant to each step (e.g., to generate alternative solutions to a personally-relevant problem), were included as part of the therapy regimen. In an attempt to facilitate maximal therapeutic gain for each patient, as well as to encourage attendance, therapists were directed to ensure that the treatment protocol be made relevant to the specific life circumstances of each individual and not simply to teach skills on a "hypothetical or conceptual level." Last, each patient was provided with written materials reflecting all aspects of PST to use as their own "self-help problem-solving manual." In particular, patients were encouraged to refer to this material between sessions and especially post-intervention. Participants in the PST condition continued to receive standard medical care regarding their cancer treatment.

The second treatment condition assessed involved PST with a significant other (PST/SO). This protocol was implemented identically to that of the PST condition except a designated "significant other (SO)" was included in the training. This SO served as a problem-solving coach by providing social support, encouragement, and feedback regarding the patient's attempts to resolve problems and cope with cancer-related stressors. SO's participated in all phases of the intervention and were provided their own set of handouts and training materials. Whereas they were encouraged to use the problem-solving principles to help cope with their own problems when necessary, the primary purpose of their involvement centered around the cancer patient. This condition was included to empirically assess whether incorporating a structured social support component in therapy would augment the effects of individually administered PST. Significant clinical experience providing PST training to family members of cancer patients to foster their own coping skills as a means of minimizing potential burnout and caregiver stress suggested to us the strong possibility of enhanced effects if PST was provided to a patient-significant other team.[54,55] Similar to the PST condition, participants in this condition continued to receive standard medical care related to their cancer treatment.

Results of this investigation at posttreatment across several self-report, clinician-ratings, and ratings by the significant other provide strong evidence in support of the overall efficacy of PST for decreasing emotional distress and improving the overall quality of life of patients with cancer. Specifically, patients in both treatment conditions were found to evidence significant improvement as compared to individuals in the control condition. At posttreatment, no differences were found between these two conditions. However, at a 6-month follow-up assessment, on approximately half of the variables assessed, patients who received PST along with a significant other continued to improve significantly beyond those individuals receiving PST by themselves, highlighting the advantage of formally including a collaborative person in treatment. These positive effects of PST were not only statistically significant, but also found to be highly clinically significant as well. Moreover, analyses indicated that improvements in problem solving were found to correlate significantly with decreases in psychological distress and improvements in overall quality of life.

4.2. Problem Solving for Caregivers of Cancer Patients

Family members who are responsible for the day-to-day care of cancer patients can also experience high levels of distress and frequent problems. As such, we have also hypothesized that training such individuals themselves in problem-solving skills may be a particularly useful approach in helping family caregivers to cope more effectively in this role.[55,56]The "Prepared Family Caregiver Course" adapted the D'Zurilla and Nezu[57] PST model as a means of providing the following types of information to family caregivers of cancer patients: (a) understanding the problem; (b) when to get professional help; (c) what can be done to deal with, as well as prevent, a problem; (d) identifying obstacles when they arise and planning to overcome them;

and (e) carrying out and adjusting the plan. Manuals have been developed that contain guided problem-solving plans across a variety of physical (e.g., fatigue, hair loss, appetite difficulties) and psychosocial (e.g., depression, anxiety) problems that cancer patients commonly experience.[58,59] These manuals use the acronym *COPE* to highlight various problem-solving operations, where C = creativity, O = optimism, P = planning, and E = expert information. Although no controlled studies have yet been conducted with this protocol, a program evaluation concerning participant satisfaction and acceptability of the treatment approach among various samples of caregivers has been very promising.[54]

5.0. IMPACT OF PROBLEM SOLVING

Others have also looked to problem-solving training as a potentially important intervention strategy to help cancer patients and their families. For example, Fawzy *et al.* developed a multicomponent treatment package that included PST and focused on patients who were newly diagnosed with malignant melanoma.[60] Cancer patients were randomly assigned to one of two conditions—a 6-week structured group intervention that included PST, stress management training, group support, and health education, and a no-treatment control. At the end of six weeks, patients receiving the structured intervention began showing reductions in psychological distress as compared to control participants. However, six months posttreatment, the group differences were very pronounced. Moreover, five years following the intervention, treated patients continued to show significantly lower levels of anxiety, depression, and total mood disturbance.[61]

In addition, at the end of the original 6-week program, patients receiving the treatment evidenced significant increases in the percentage of large granular lymphocytes, suggesting a positive treatment effect on immune functioning. Further, six months posttreatment, this increase in granular lymphocytes continued and increases in natural killer cells were also evident. Last, although not originally structured to determine the effects of treatment on actual health outcomes, it was found six years posttreatment that treated patients experienced longer overall survival as compared to control participants, as well as a trend for a longer period to recurrence for the treated patients.[62] This same intervention was later adapted for a Japanese population and found to be effective for Japanese women with breast cancer.[63]

Mishel *et al.* paired training in problem solving with a cognitive reframing strategy as a means of helping 134 Caucasian and 105 African-American men with localized prostate carcinoma to manage their levels of uncertainty and symptom control.[64] Participants were randomly assigned to one of three experimental conditions—the combined psychosocial treatment provided only to the patient himself, treatment provided to the patient and a selected family member, and the control ("medical treatment as usual"). Both forms of treatment were provided by trained nurses through weekly phone calls for eight weeks. In general, regardless of ethnicity, participants who received either form of the intervention improved significantly as measured at the 4-month post-baseline assessment. It is during this period of time that cancer treatment side effects are most prevalent. As such, it is particularly noteworthy that the combined PST and cognitive reframing treatment led to significant improvement in control of incontinence at 4-months post-baseline.

Allen *et al.* assessed the efficacy of PST, as compared to a no-treatment control, with regard to a population of 164 women diagnosed with breast cancer and for whom a first course of chemotherapy had been recently initiated.[65] PST consisted of two in-person and four telephone sessions with an oncology nurse who provided problem-solving skills training to the women over a 12-week period. This treatment program was designed to empower women with breast carcinoma to cope more effectively with a range of difficulties when diagnosed in mid-life. Participants in both conditions were assessed for physical and psychosocial adjustment.

At a 4-month evaluation, participants in general tended to have significantly less unmet needs and better mental health as compared to baseline. At the 8-month assessment, differences between the treated and control conditions emerged, pointing to the efficacy of the training. In general, PST led to improved mood and more effective coping with problems associated with daily living tasks. Further, the intervention was effective for the majority of women in resolving a range of problems related to cancer and its treatment, including physical side effects, marital and sexual difficulties, and psychological problems. However, an unexpected finding emerged with regard to women who had baseline scores characteristic of "poor problem solving." In essence, such individuals, relative to the control participants, were less likely to resolve such cancer-related problems. Qualitative analyses suggested that such individuals became especially overwhelmed by expectations to "go it alone" after only one in-person treatment session. As such, these authors concluded that an important outcome of this study was the advisability of prescribing treatment based on one's level of need or risk. In other words, for individuals who are initially identified as poor problem solvers, a more intensive program (e.g., more face-to-face sessions) may be necessary as compared to those who at baseline are average or good problem solvers.

A study by Given *et al.* focused on 237 adult cancer patients recently diagnosed with a solid tumor and who were undergoing a first course of chemotherapy.[66] Participants were randomly assigned to either a "symptom management intervention" or conventional care. The cognitive–behavioral intervention was based on the PST model of D'Zurilla and Nezu[67] in order to generate a listing of possible strategies to provide to patients and their caregivers in order to more effectively cope with a variety of cancer-related problems (e.g., alopecia, depression, fatigue, pain, insomnia). Based on discussions between a nurse and patient-caregiver dyad, various interventions were selected for implementation. Treatment occurred within ten contacts (in person and telephone) over the course of 20 weeks.

Results indicated that treated patients who had higher baseline symptom severity levels reported lower depression at ten, but not 20 weeks. Unexpectedly, patients in the experimental condition characterized by higher baseline depression were found to be more depressed at ten weeks that control patients. Further, the intervention was found to be more effective in lowering depression at ten weeks as a function of its impact on other symptoms rather than on depression directly. However, at 20 weeks, a significant main effect for treatment on depression was not identified. As such, these authors concluded that the intervention influenced depression differentially over time. Specifically, it appeared to lower depression through enhanced ability to manage symptoms unrelated to depression and only later did it impact depression directly.

In a subsequent assessment of the impact of this intervention on the limitations imposed on patients by symptoms of cancer and its medical treatment, Doorenbos *et al.* recently reported that on average, after ten weeks, patients receiving the problem-solving based intervention reduced such symptom limitations by a statistically significant 13 points more than the control group.[68] Moreover, this positive treatment effect was maintained over the course of the remainder of the treatment. Parenthetically, these authors concluded that this intervention was particularly helpful for younger individuals in managing cancer-related symptom limitations.

With regard to problem-solving interventions for family caregivers of cancer patients, Toseland *et al.* reported a study that evaluated the efficacy of an intervention for spouses of cancer patients that included support, problem-solving, and coping skills.[69] Forty male and forty female spouses of cancer patients were randomly assigned to this intervention or a "usual treatment" condition. Results indicated that little change occurred over time for caregivers in either the treatment or control condition. However, this lack of effects were probably due to the low level of distress and problems that existed across this sample at pretreatment. Thus, when focusing on a subsample of distressed caregivers, significant effects were in fact evident. For example, distressed caregivers undergoing the PST-based intervention were found to significantly improve in their physical, role, and social functioning, as well as their ability to cope with pressing problems. The actual cancer patients related to this subsample of distressed caregivers receiving the intervention were also found to be significantly less depressed at posttreatment. Moreover, in a subsequent 6-month post-baseline follow-up, it was found that, overall, patients whose spouses received the PST intervention became significantly less depressed than did control patients.[70]

Schwartz *et al.* assessed the impact of a brief PST intervention regarding cancer-specific and general distress among 341 women with a first degree relative who had recently been diagnosed with breast cancer.[71] This investigation included two conditions: PST and a general health counseling (GHC) protocol. Both interventions were conducted during a single 2-hour individual session with a health educator. Initial analyses indicated that both approaches equally led to decreases in cancer-specific and general distress. However, when PST participants were divided into those who practiced the skills and those who did not, significant differences did emerge. Specifically, "PST-practicers" had significantly greater decreases in cancer-specific distress compared to both "non-practicers" and GHC participants. In addition, controlling for baseline education and distress differences between the groups did not reduce the magnitude of these results.

Adding to this same sample to eventually include 510 women who had a first-degree relative with breast cancer, a different question was now asked—does a brief PST intervention increase the likelihood of adherence to breast self-examination?[72] Whereas initial results found no differences between conditions, a cancer-specific distress by treatment interaction was identified. Specifically, among women who participated in the PST condition, those with high levels of distress were two times more likely to improve in adherence than women low in cancer-specific distress. No such effect was identified among control participants. The authors suggest that women with a family history of breast cancer who have high levels of distress may be most likely to benefit from PST when attempting to promote adherence to breast cancer screening.

Sahler *et al.* focused on the well-being of mothers of newly diagnosed pediatric cancer patients.[73] Ninety-two such mothers were randomly assigned to one of two conditions—PST and a control (standard psychosocial care). The problem-solving intervention consisted of eight 1-hour individual sessions and was adapted for this population based on the work of D'Zurilla and Nezu.[67] At posttreatment, results indicated that mothers in the PST condition has significantly enhanced problem-solving skills and significantly decreased negative affectivity as compared to their control counterparts. Moreover, analyses revealed that changes in self-reports of problem-solving behaviors accounted for 40% of the difference in mood scores between the two conditions. In addition, the intervention appeared to have the greatest impact on improving constructive problem solving, whereas improvement in mood was most influenced by decreases in dysfunctional problem solving.

In an extension of their previous investigation, Sahler *et al.* further assessed the efficacy of PST among a sample of 430 English- and Spanish-speaking mothers of pediatric cancer patients.[74] Again, the 8-week PST condition was compared to a usual care control. Replicating their previous work, results from this study indicated that mothers receiving the PST protocol reported significantly enhanced problem-solving skills and significantly decreased negative affectivity. Whereas treatment effects appeared to be greatest at posttreatment, several differences were maintained at the 3-month follow-up. Interestingly, the efficacy of PST for Spanish-speaking mothers exceeded that for English-speaking mothers. Moreover, results suggest that young, single mothers befitted the most from the problem-solving intervention.

6.0. NEW DIRECTIONS FOR FUTURE RESEARCH

Based on our review of the general literature regarding psychosocial interventions for the treatment of stress, anxiety, and depression among cancer patients, we offer several recommendations for future research that focus mainly on intervention studies.

1. *More research should be conducted regarding efficacious interventions to improve the quality of life of cancer survivors and their families.* Although a substantial body of research already exists, we need to know more about what types of treatment approaches are effective for what types of patients as a function of type of cancer, stage of cancer, socioeconomic status, ethnic background, level of stress experienced, where in the continuum of survivorship and other important patient-relevant psychosocial variables. Because of the significant personal, medical, and economic impact cancer and its treatment represents, more research evaluating the efficacy of a wide range of psychosocial strategies should be conducted in the future.

2. *More research should be conducted regarding the effects of psychosocial interventions on health outcome (i.e., prolonged survival).* Currently, the literature is equivocal in its ability to indicate whether psychosocial treatments can have an impact on health outcome, particularly with regard to prolonging the life of a cancer patient.[23] While well-controlled investigations capable of addressing such a question requires extensive resources, preliminary results suggest that such efforts may be worthwhile.

3. *Improve the methodological rigor of the research.* Because a thorough critical analysis of the literature was beyond the scope of this chapter, we did not document the many methodological limitations identified across studies. We will not belabor the point, except to list specific recommendations: (a) include adequate control groups; (b) use manualized protocols; (c) include treatment integrity (i.e., therapist adherence and competence) measures; and (d) use more multi-modal assessment procedures (e.g., multi-trait, multi-method approaches) for outcome measurement. In addition, special care needs to be taken in describing each population under study in detail in order to better allow for meaningful comparisons across studies.

4. *Conduct component analyses of the intervention studies.* Beyond simply comparing an intervention to either an alternative treatment approach (e.g., education) or a control condition (e.g., waiting-list), additional research strategies should be implemented to help answer the question “which treatment components are responsible

for the actual improvement in symptoms?" Future research needs to be more explicit in delineating specific treatment strategies and provide for an assessment of the specific impact of a particular intervention on a given hypothesized mechanism of action and its resulting impact on changes of interest. In that manner, a more comprehensive and microanalytic understanding of cause-effect relationships can be obtained.

5. *Identify important moderators of treatment efficacy.* Identification of important moderator variables (e.g., race, age, gender, cultural background, severity of symptoms, number of symptoms) can potentially lead to better matching of a given treatment for a particular patient, as well as the development of more effective interventions per se.

6. *Identify important mechanisms of action.* Future research should also address the relationship between outcome (e.g., psychological well being, improved health) and a variety of variables (e.g., cognitive, emotional, behavioral, immune system function) hypothesized to contribute to the etiopathogenesis and course of that outcome. In this manner, salient treatment targets can be identified and more empirically-based decisions about treatment design can be made.

7. *Improve treatment implementation and access.* Related to the issue of health economics, future research should also attempt to save costs directly related to implementing psychosocial interventions. Having a doctoral-level psychologist, for example, providing individual or group therapy to cancer patients and their families is likely to be viewed as too high a price to the health care delivery system. As such, studies geared to assess alternative means of conducting psychosocial interventions should be conducted in the future. For example, additional methods exist to conduct such treatment approaches besides the traditional use of a single therapist in face-to-face situations. Use of videos, computers, the internet, or telemedicine support systems represent further possibilities regarding ways to cut costs, as well as to increase accessibility to patients not living close to a major medical center.

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Chapter 19

Managing Daily and Long-Term Stress

Linda E. Carlson and Michael Speca

1.0. SURVIVORSHIP

Effective management of the consequences and sequelae of cancer diagnosis and treatment is becoming more important as the number of cancer survivors has become a top priority of health care. Certain symptoms are common after cancer treatment. We have grouped these into four categories for the purposes of this chapter. These include: (1) Symptoms of distress; (2) Problems relating to sleep difficulties and persistent fatigue; (3) Existential and spiritual issues, and; (4) Persistent underlying biological changes that may result in increased risk for other diseases or cancer recurrence. Each area will be summarized but not reviewed exhaustively.

2.0. CONCOMITANTS OF CANCER SURVIVORSHIP

2.1. Distress

In addition to the documented prevalence of clinical depression and other types of behavioral health problems, many more survivors report feelings of distress, daily or episodically. Distress is generally defined as "a multi-determined unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and spiritual crisis."[1] Although usually not as severe as a psychiatric diagnosis of anxiety or depression, the prevalence rates of distress are even higher.

A large study of 4496 cancer patients found an overall prevalence rate of significant distress of 35.1%, with the greatest distress in lung cancer patients (43.4%), followed by brain, Hodgkin's disease, pancreas, lymphoma, liver, head and neck, breast, leukemia, melanoma, colon, prostate, and finally gynecological (29.6%) cancers.[2] Another recent large-scale study targeting all patients visiting our tertiary cancer center assessed over 3000 cancer patients, and found that 37% met criteria for significant distress on the Brief Symptom Inventory.[3] More pertinent to this volume, in our study, even those who were reporting to the center for follow-up cancer care and had completed active treatment had elevated distress levels, with 34.4% scoring over the cut-points for significant overall distress. This is not a phenomenon exclusive to cancer patients in North America, as similar overall rates were reported in several European countries,[4–6] the Middle East,[7–9] South America,[10] and Asia.[11,12] These findings highlight the need to address continuing symptoms of distress among cancer survivors as they move forward in their recovery.

Based on these and other data, distress has been endorsed at the 6th Vital Sign in cancer care (following temperature, respiration, heart rate, blood pressure, and pain) by accreditation organizations and journals such as the *Journal of Clinical Oncology*[13] and *Psycho-Oncology*.[14] It has also been recommended in a *Lancet* editorial that distress be treated as a critical element in cancer care, and assessed at every follow-up visit,[15] just as one would assess the other vital signs. Methods and models for such efficient distress screening have been published.[1,16]

2.2. Sleep and Fatigue

The importance of sleep and the treatment of sleep disturbance during and after cancer treatment have been relatively overlooked, although the area is beginning to receive more attention.[17,18] In one study, over half of a sample of women with breast cancer reported symptoms of insomnia and 19% met the criteria for clinical insomnia.[19] Furthermore, 58% of the patients attributed cancer as the cause of or aggravating their sleep difficulties. These prevalence rates are double those in the general population, with insomnia rates ranging from 9% to 12%. Other research has found similarly high rates of sleep disturbance in cancer patients, ranging from 45%[20] to 75%,[21] depending on the sample and method of assessing sleep disturbance. A study comparing breast cancer survivors with hot flashes to healthy matched control women found that sleep disturbance rates were high in both groups (73% of cancer survivors and 67% of matched controls), but survivors had a shorter duration of sleep.[22] Once sleep patterns are disrupted, sleep disturbance often persists after cancer treatments are complete and may require interventional remediation.[17]

Fatigue, too, is common and debilitating. The term cancer-related fatigue (CRF) has been recognized and is defined by the National Comprehensive Cancer Network as "a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning."[23] It can persist over time and can interfere with usual activities. As was discussed in the chapter on fatigue mechanisms, this fatigue is different from that of everyday life, which is usually temporary and relieved by rest. Cancer-related fatigue is more severe and more distressing, and rest doesn't always relieve it. Fatigue was the most common symptom experienced by almost half of all patients we surveyed at the TBCC in 2003.[3] Over 43% of nearly 1400 survivors at the center for follow-up visits still reported fatigue as a problem. In fact, 30–75% of all cancer survivors report fatigue continuing for months or years after completing active treatment,[23] and 45% of patients believed that nothing could be done to relieve or reduce fatigue.[24] Patients perceive fatigue to be the most distressing symptom associated with cancer and cancer treatment, rating it as more distressing than pain, nausea, and vomiting.[25] In the context of this book it is important to highlight that this fatigue can be episodic, recurrent and chronic years from initial treatment.

A longitudinal study of over 700 breast cancer survivors found that approximately 34% reported significant fatigue 5–10 years post-diagnosis, which was no lower than the prevalence in the same women 1–5 years after diagnosis.[26] Fatigue disturbs the patient's quality of life and ability to function on a daily basis.[27] It may be the predominant factor preventing many cancer survivors from living a fulfilling and satisfying life following the completion of treatment. It may seem logical to impute a relationship between sleep disturbance and fatigue, as poor sleep may lead to increased fatigue. However, some studies have found sleep disturbance to be independent from levels of fatigue.[28] The relationship between sleep disturbance and fatigue certainly merits further investigation. Regardless, the implementation and study of behavioral interventions to address sleep disturbance and fatigue in the survivor population are sorely needed.

2.3. Existential and Spiritual Issues

Considering existential issues, a heightened awareness of mortality and death is typically evoked in persons diagnosed with cancer. But rather than being a wholly traumatic experience, cancer can signal a life transition offering the possibility of both positive and negative psychosocial outcomes. Many people diagnosed with cancer describe personal growth consequent to their illness experience.[29] Those impacted by challenging life events like cancer often perceive associated benefits such as improved relationships, greater appreciation of life, and increased resilience. Such benefit finding has piqued much recent research interest.[30–33] Indeed, diagnosis may actually provoke patients to initiate an inner quest for greater clarity and a renewed sense of meaning and a purpose in life. Several researchers have proposed that people often make sense of their diagnosis by construing beneficial consequences of their predicament.[34–36] Here we use the term post-traumatic growth (PTG) to refer to the discovery or process of searching for benefits or positive implications of the cancer experience and related life changes.

There has been a recent surge of research investigating PTG in cancer patients. One study found that patients undergoing consideration for bone marrow transplantation met or exceeded a matched control group on measures of positive psychosocial change, even though they rated their physical and functional ability to be declining.[34] Also, breast cancer patients had significantly higher scores in PTG than a group of age and education-matched controls, specifically in the areas of relating to others, spirituality, and appreciation of life.[37] A third study found that women with breast cancer reported significant improvements, above those of women with benign breast problems, in their outlook on life, love for their spouse or partner, religious satisfaction, and spirituality.[38] These results, too, were apparent despite reports of poorer health and physical functioning.

PTG and spirituality appear to be closely related constructs. Although spirituality is challenging to define, it often includes dimensions such as meaning making, faith, purpose, and connection with others and a higher power.[39,40] Spirituality differs from religiosity, in that it is not necessarily specific to a particular theological framework; hence it is a more inclusive term.[41] A review of the literature on spirituality emphasizes its importance in helping people to adapt and adjust to cancer.[42]

Furthermore, there seems to be some conceptual overlap between PTG and spirituality. Indeed, spirituality and benefit finding increased in tandem as measured in one study, indicating that these variables may share a significant correlational relationship.[43] Patients who scored high in benefit finding had increased skills, felt a sense of purpose, had closer relationships, better coping, increased spirituality, and an overall deeper appreciation of life. While there is some evidence that benefit finding and spiritual well-being increase with the diagnosis of cancer itself,[35] it is not known if PTG or spirituality can be facilitated through psychosocial interventions. There are some preliminary indications that this may be possible.[44]

2.4. Biological Consequences

The process of recovery from cancer is also affected by the impact of cancer and its treatment on fundamental biological functioning, which in turn can be affected by psychological factors such as stress. One study tracking cancer survivors found higher incidences of lung disease, heart disease, pain syndromes, and obesity.[45] Cancer survivors are more likely than the general population to report being in only fair or poor health, and to have functional and work limitations.[46,47] Many cancer survivors eventually die of diseases other than cancer, heart disease being most prevalent. Hence, cardiovascular health is an important consideration for cancer survivors. Cancer patients are at increased risk for cardiac toxicity and damage as a result of primary treatments. Cardiac toxicity is a well-established side-effect of anthracyclines, which are increasingly used in adjuvant therapy of many cancers.[48] In addition, radiation- and chemotherapy-related heart disease can lead to congestive heart failure.[49,50] Treatment-induced heart damage may become evident years after therapy has been completed[51] and there are indications that heart-related side effects of primary cancer treatment can have a dramatic impact on both quality of life and patient survival.[50] Thus, it is particularly important to monitor cardiac health in cancer survivors, an aspect of overall health that may be benefited via stress-reduction interventions.

Cancer survivors, by virtue of persistent high levels of both physical and psychological stress, may also be susceptible to the adverse biological effects of elevated stress-related hormones, such as excessive cortisol secretion (e.g., ref. 52) and production of catecholamines such as adrenaline.[53,54] Sustained increases in stress hormones can in turn have inhibitory effects on functional immunity.[55] For example, elevated cortisol secretion can decrease antibody production, and inhibit natural killer (NK) cell activation,[56–58] important aspects of immune functioning that may protect cancer survivors from disease recurrence and other infections. Not surprisingly, compromised immune and neuroendocrine function have been noted in cancer patients (e.g., refs. 59–63), features inimical to recovery from disease. In addition, elevated basal cortisol levels and blunted cortisol responses to acute stress tasks have been observed among some individuals with cancer,[64–66] and have been associated with earlier mortality in metastatic breast cancer patients.[67]

Hence, survivors who have dysregulated neuroendocrine function may be at higher risk for cancer recurrence as well as morbidity and mortality from other causes related to immune system impairment. In sum, for cancer survivors who are at high risk for future health problems, stress-reduction interventions that effectively counteract maladaptive cardiovascular and neuroendocrine function may demonstrate value in terms of mitigating these threats to long-term health.

3.0. THEORETICAL APPROACHES TO STRESS REDUCTION IN SURVIVORS

In the Chapter by Lent a model for restoring emotional well-being is presented. He refers to Ryan and Deci's concepts of hedonic vs. eudiamonic perspectives of well-being, wherein well-being is attributed to either to the valance between positive and negative affect, or the quest to achieve growth, purpose, and meaning in one's life, respectively. Lent relates the hedonic view to the development of research on subjective well-being, while the eudiamonic position is more pertinent to the study of psychological well-being. He further suggests that enhancing psychological well-being may be the central route to improving subjective well-being. The approach taken in the previous chapter by Nezu and Nezu focuses primarily on directly improving the subjective well-being of cancer survivors through the means of problem-focused coping and problem-solving therapy, which has a good deal of research to support its efficacy. This approach primarily focuses on targeting specific aspects of the three components of subjective well-being outlined by Lent: life satisfaction, positive affect, and negative affect. Beneficial shifts in these components are accomplished through teaching coping and appraisal strategies to enhance coping skills and problem-related coping efficacy, as illustrated in Lent's model.

In the current chapter, although there is unquestionably some overlap, we will focus on interventions that place somewhat greater emphasis on the emotion-focused end of the coping spectrum, which more often subscribe to a more eudiamonically-oriented approach to achieving well-being, that is, by aiming to uncover meaning and purpose in one's life, rather than exclusively teaching cognitive coping strategies. The underlying aim is to establish and elaborate a framework of eudiamonic well-being that will persist regardless of fluctuations in day-to-day subjective well-being or hedonic happiness. Although it is theoretically appealing to apportion coping and well-being into such categories, undoubtedly the stress-reduction interventions discussed in this chapter act on many levels to support symptom reduction and enhanced well-being.

4.0. INTERVENTION RESEARCH

Several approaches intended to reduce stress primarily through emotion-focused coping have been investigated. Emotion-focused coping refers to dealing directly with the emotional concomitants of life events, such as distress and existential angst, rather than trying to solve the problem directly—it is useful in circumstances when one has little or no control over the specific situation, such as fears of cancer recurrence or death and dying.[68] Our experience is predominantly in the application of mindfulness-based stress reduction (MBSR). However, before reviewing this research in detail, we present an overview of several other approaches that have shown some benefit for cancer survivors. The three approaches we summarize are cognitive–behavioral stress management (CBSM), supportive–expressive group therapy (SEGT), and creative arts interventions.

CBSM was developed by the Miami Behavioral Medicine group in the 1980s to help people diagnosed with AIDS cope with the demands of chronic illness. The 10-week group program is manualized and structured, and covers a variety of areas including stress awareness, aspects of cognitive–behavior therapy such as identification of automatic thoughts and cognitive distortions, physical relaxation and breathing techniques, meditation, social support, anger management, and assertiveness communication training. It has since been reformulated for application to cancer populations and a manual on CBSM specifically for the treatment of breast cancer published by the American Psychological Association.[69]

The CBSM program has been applied to groups of women with breast cancer and men with prostrate cancer by the Miami group. They found that CBSM compared to a 1-day stress management seminar decreased depression, improved emotional processing, and increased optimism and a sense of benefit of having gone through the cancer experience in women with early stage (0-II) breast cancer.[44] They also investigated biological outcomes and found that women assigned to CBSM showed decreases in cortisol levels after group completion,[70] and increases in immune cell response to a T-cell challenge at the end of adjuvant therapy.[71] In addition, the physiological changes were greatest in those women who showed the most psychological improvements. In the longer term, women in CBSM showed a stronger immune response of NK cells up to 6 months after completing the CBSM intervention. In men with prostate cancer, similarly, CBSM improved quality of life, enhanced benefit finding and improved stress management skills.[72]

SEGT is a form of professionally led group psychosocial intervention that evolved specifically to address the support needs of seriously ill medical patients. Two key interrelated goals of SEGT are to build social bonds and to facilitate the expression of emotion. Within the supportive context of the therapy group, patients are encouraged to express the full range of authentic feelings they are experiencing as they confront the existential reality of living with a life threatening and often debilitating illness. The adaptive function of emotions is validated and a shared group ethic of acknowledging and expressing emotion serves to normalize expectable reactions of fear and sorrow. This frees patients from harmful, emotionally stultifying social proscriptions against expressing what are commonly seen as negative emotions and unconsidered, though well-meaning, exhortations to “keep positive.” Other goals of SEGT include detoxifying illness and death, redefining life priorities, improving coping, enhancing the doctor–patient relationship, and fortifying existing networks of friends and family. Thus, the group becomes a vessel for the expression, containment, and processing of current distress. At the same time, ample scope is provided to explore the longer-term meaning and implications of living with a serious or life-threatening medical condition. This enables patients and their families to proactively address foreseeable challenges, to marshal appropriate resources and to make the most of whatever life remains.[73]

Though an early finding of extended survival for metastatic breast cancer patients enrolled in a supportive–expressive group[74] was not replicated in the large breast expressive–supportive therapy pan-Canadian trial (BEST[75]), success of the approach in alleviating pain and suffering, as well as enriching the lives of patients diagnosed with metastatic cancer, has led to successful utilization of the therapeutic model for patients with early stage breast cancer[76] and investigations of its applicability for patients diagnosed with a range of other serious illnesses (see ref. 77).

The third area of interest encompasses a variety of interventions based on principles affirming the healing capacity of creative activity. Creative therapies for cancer patients are generally intended to integrate physical, emotional, and spiritual care by facilitating creative ways for patients to respond to their cancer experience.[78] Some have suggested that by offering opportunities to engage in the arts and creative expression, persons with cancer can be enabled to mourn, grieve, celebrate life, be empowered to endure their situation, and find healing and meaning.[79] The overall mission of one program was stated as the identification and development of connections between the creative arts and the healing arts that improve the physical, mental, emotional, and spiritual health within the community.[80] The basic assumption underlying this program was that creating opportunities to explore artistic expression without judgment or criticism can lead to greater self-awareness and self-esteem and can stimulate innate creative and healing processes. Similarly, the stated goals of another program developed cooperatively by artists and health care professionals were to: (1) provide an environment that develops into a nurturing community; (2) create opportunities for emotional healing; (3) help participants to find meaning in their experiences; and (4) promote creativity as a vehicle for self-knowledge through the creation of a piece of artwork.[81]

However, although there are many descriptions of various programs in the literature, with content ranging from the visual arts[82] to dance,[83] music therapy,[84] creative writing,[82] and mixed-modality programs,[78,80] few have included rigorous evaluation components. Benefits that have been reported from creative therapy programs include social support, psychological strength, and new insights about the cancer experience.[79] Research on expressive writing paradigms have supported its benefits in groups of medical patients,[85] and in another study, cancer patients who wrote about their cancer experience reported significantly less sleep disturbance, better sleep quality and sleep duration, and less daytime dysfunction than those who wrote about a neutral experience.[86] Additional well-controlled research in creative arts therapies utilizing visual arts, sculpture, music, and dance are needed.

5.0. MINDFULNESS-BASED STRESS REDUCTION

Another approach that has been used to help cancer survivors cope with many of the common posttreatment problems detailed above is MBSR. Mindfulness itself stems from Eastern meditation practices, and has been described as nonelaborative, present-centered awareness in which each thought, feeling and/or sensation that arises in the attentional field is acknowledged and accepted nonjudgmentally as it is. Recent attempts at definition have resulted in a two-component model of mindfulness.[87] The first component involves self-regulation of attention on immediate experience, resulting in recognition of events arising in present moment awareness. The second component represents an orientation of openness and acceptance of moment-to-moment experience. This is similar to another suggested conceptualization of mindfulness as composed of intention, attention, and attitude.[88] Intention in this model describes the purposive nature of directing the faculties of attention toward observing moment-to-moment experience, parallel to the first component in Bishop *et al.*[87] The third attribute, attitude, describes the quality of the attention, one of gentle, nonjudgmental acceptance of whatever arises in the field of awareness, similar to Bishop *et al.*'s second component.[87] Thus, in both these conceptualizations, mindfulness involves not only paying attention, but doing so in a way that encompasses attitudes of nonjudging and open acceptance.

Mindfulness provides the practitioner with an active method to turn off the pervasive reactivity that is common to many Westerners and replace it with conscious responses. Mindfulness is cultivated by practicing various forms of meditation, or mental training. These can be performed in formal meditation sessions, or during

Table 1. MBSR Attitudes

Attitude	Description	Basis
Nonjudging	Applying openness to experience and not judging experience as good or bad, but seeing things clearly as they are in each passing moment	Judging (particularly self-judging) happens constantly and leads to demoralization and limitation of options
Beginner's mind	Seeing things as if for the first time—discarding old labels and allowing for fresh possibilities in each moment	Labeling and categorizing leads to restricted behavioral options and reinforces old maladaptive patterns of behavior
Patience	Waiting for events to happen in their own time without getting agitated, restless and impatient	Acknowledges there are many things that take time to unfold and can't be forced
Trust	Trusting one's own intuition and the basic goodness and wisdom of being	Allows one to open to one's own intuition and release suspicion and distrust, relaxing into a place of safety
Acceptance	Accepting things one cannot change with equanimity—moving beyond denial and seeing things clearly as they are	Refusing to acknowledge things as they are leaves one stuck in delusion and limits effective options for genuine change
Letting go	Letting go of trying to control things that are outside of one's ability to control—going with the flow	Recognizing that the vast majority of events are not under individual control is freeing and doesn't lead to intolerable fear or anxiety
Nonattachment	Not being attached to outcome—whether considered good or bad. Releasing tendencies to grasp at or try to force certain outcomes	Based on the concept of equanimity and realization of the constantly changing nature of all experience including the self

day-to-day activities, such as washing the dishes, simply by being present in the moment while allowing oneself to experience it in its fullness. Several key attitudes conducive to training in mindfulness, including nonjudging and acceptance, and the theoretical basis for their incorporation into the practice are described in Table 1.

Cultivation of mindfulness involves paying attention to the habitual wanderings of the mind, and learning to shift out of the typical mode of mental rumination on abstract thought with a past or future focus, back to here and now experience. Excessive focus on the past often leads to feelings of regret, anger and sadness, and an exclusively future orientation can promote worry and anxiety—in either case one misses the living of life that occurs only in the present moment. The consequences of being aware of the workings of the mind in a supportive and accepting environment and learning to shed the consequences of attachment to self-limiting conceptual frameworks, include cultivating a sense of freedom, peace and expansive connection with others and with nature.

Mindfulness practices have been incorporated into mainstream health care through the MBSR program format developed by Jon Kabat-Zinn and colleagues at the Stress Reduction Clinic of the University of Massachusetts Medical Centre in the late 1970s.[89,90] They applied a behavioral medicine model and initially offered the program to populations with a wide range of chronic pain and stress-related disorders who typically were experiencing suffering that was unrelieved by conventional medical treatment. In designing the program, Kabat-Zinn integrated mindfulness meditation and gentle hatha yoga into a secular program that could be taught to people facing diverse health issues and with no prior meditation experience.[90] Mindfulness is the overarching theme of the program, which is applied to a variety of activities including mindful movement and body awareness, several forms of meditation practice, group discussion, and mutual support. The format is 8-weeks of 2.5–3 hour weekly group sessions, with a 6-hour silent retreat on the Saturday between weeks 6 and 7. Participants also commit to approximately 45 minutes of home meditation and yoga practice 6 days a week throughout the program, and are provided with audio CDs of guided meditations and yoga exercises.

MBSR as we have been offering it to cancer survivors at the Tom Baker Cancer Centre in Calgary, Canada, differs somewhat from the Centre for Mindfulness format, in that the sessions are shorter (1.5 hours each) and our Saturday retreat has been only 3 hours. These modifications were made in deference to the high levels of functional impairment, weakness and fatigue of our participants, many of whom are on active treatment. We have also incorporated specific yogic sleep exercises (in response to observed high rates of sleep disturbance in our population) and breathwork. Cognitive behavioral stress management principles are examined in the context of mindfulness and discussed in more depth than in traditional programs. The primary focus and stance of the program on mindfulness, however, is entirely congruent with the original MBSR intervention.

6.0. APPLICATION OF MBSR TO CANCER SURVIVORS

Training in mindfulness meditation develops the capacity for the intentional self-regulation of attention and applies this capacity toward the cultivation of insight regarding the basic processes through which each of us construe identity and meaning from experience. The skills and understandings thus developed have broad applicability for cancer survivors, which include but are not limited to the goal of stress reduction.

A principal aspect of mindfulness meditation that has particular salience for cancer patients is its here and now orientation, that is, the radical insistence on paying attention to present moment experience. Some sources of stress for cancer patients relate to the past. These might include attributions about cancer causation, regrets about past decisions or life priorities, and concerns about the future. Other worries also relate to future expectancies regarding health such as enduring pain or suffering or the loss of life itself. The practice of mindfulness provides an effective antidote to these sources of stress, which lie primarily in memory and imagination, by anchoring awareness in the present and providing a relatively conflict-free sphere from within which the nature of disturbing thoughts and emotions can be examined, understood, and integrated.

Many cancer patients' initial interest in MBSR derives from their suspicion that their cancer was caused by stress, emotions, or other psychological factors. Though causal relationships between these factors and cancer initiation or progression have not been convincingly demonstrated,[91,92] this is a notoriously difficult area of study and in the absence of definitive science many patients are determined to explore these connections as they may relate to their own life situation. MBSR, with its holistic orientation to healing provides a framework for these patients' explorations as they experience and directly observe the relationships between their behavior, thoughts, and feelings and bodily responses. Didactically presented information relating to physiologic functioning and the stress response cycle also supports their quest for knowledge of mind–body medicine. Though MBSR promotes an orientation of non-doing, highlighting awareness of being rather than goal-oriented behavior, patients do often learn experientially how to moderate their level of arousal. This knowledge assists them to manage daily stress effectively and to assume an active role in their own healing process.

The frank uncertainty cancer brings into the lives of those affected poses an immense challenge to preexisting perceptions of personal control over one's future and one's own body. Such perceived loss of control and questioning or uncertainty regarding one's sense of self-efficacy are strongly associated with psychological distress and diminished psychosocial adjustment to cancer.[93,94] MBSR addresses these factors in several ways. Adopting the attitude and practice of acceptance, that is, holding experience in awareness while relinquishing identification with the felt imperative to react or respond, frees patients from unrewarding efforts to control the uncontrollable. Attachment to threatened aspects of the conditioned temporal sense of self, one's social identity, is softened by a growing understanding that we embody deeper currents of being whose sources we share with the larger universe. Facing and accepting the totality of one's experience as it is, including losses and limitations, provides an authentic foundation for expressions of personal choice and control that can enhance self-efficacy in meaningful domains of experience such as self-care and relating to others.

Because the practice of mindfulness involves acceptance and acknowledgement of things as they are but encourages us to experience them with beginner's mind, that is, devoid of preconceptions and expectations, the wide range of possibilities inherent in each moment of life become more apparent. New options for perceiving, understanding and responding to one's life situation can be apprehended, which heightens both one's sense of freedom, as well as responsibility for choices that are made. Thus survivors can divest themselves of preconceptions that may limit their capacity to see potentially positive outcomes as they move forward in their journey.

7.0. EMPIRICAL SUPPORT FOR MBSR IN CANCER SURVIVORS

Our first study of MBSR specifically for cancer patients was also the first published in the scientific literature, in the year 2000, so this area is still in its infancy. Nonetheless, a growing body of empirical support indicates that MBSR may be helpful to survivors in ways that would theoretically be expected. A recent review paper of MBSR studies in cancer[95] joins several prior review papers which document what is known about the efficacy of mindfulness-based interventions within diverse patient populations.[96–98] The following overview is structured to coincide with the four categories of symptoms pertinent to cancer patients described in the first section.

The review will highlight specific aspects of a conceptual model presented in Figure 1. This model, guiding our thinking about the role of MBSR in a health psychology context, is based on a general biobehavioral or biopsychosocial approach. A number of authors have published similar models[99–101]—Figure 1 is our adaptation, specific to MBSR, showing in simple terms our understanding of interactions among a number of key elements, many of which we have already discussed in this chapter. It includes the influence of psychological, social and biological background variables

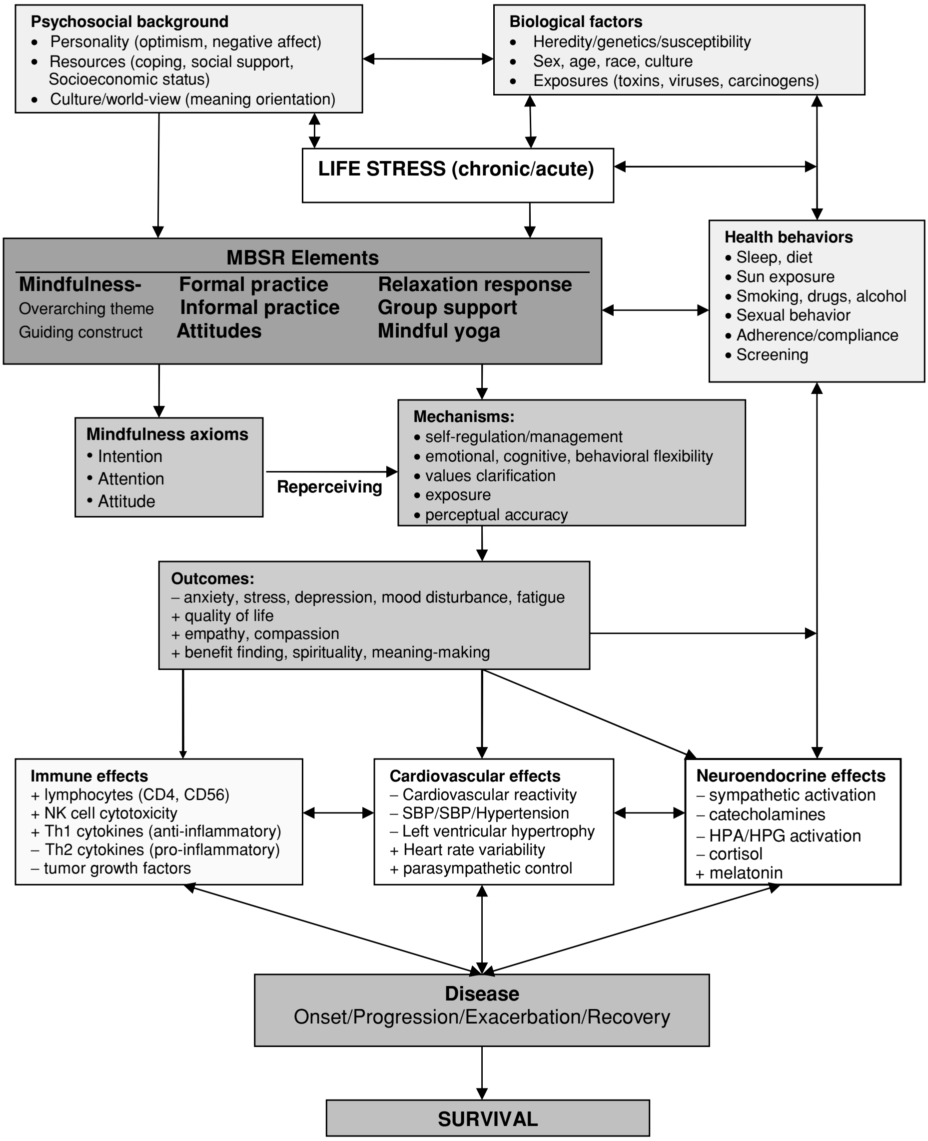

Figure 1. Biobehavioral Model of MBSR.

such as temperament, social support, and heredity, as well as health behaviors such as diet, exercise and smoking, on health outcomes. These factors interact with the experience of life stress, which can in turn influence neuroendocrine, immune and cardiovascular processes that effect disease course and recovery. The MBSR intervention can act through mindfulness to affect psychological processes as indicated, and change health behaviors, both of which may impact biological processes. These in turn affect disease processes and subsequent morbidity and mortality.

This model serves to indicate potential pathways and mechanisms through which psychosocial interventions, particularly MBSR, may influence health. It also summarizes the findings of a number of lines of research, including our own—other theoretical associations are indicated which have not yet been empirically tested.

7.1. Distress and Quality of Life

We published, in 2000, a randomized clinical trial comparing MBSR to a waiting-list control group for a mixed group of cancer patients, some of whom were on active treatment and some who were beyond the treatment phase.[102] Patients in this study had a wide range of cancer diagnoses of all stages, and were not restricted in terms of treatment-related variables. Following the intervention, participants in the intervention group had significantly less overall mood disturbance, less tension, depression, anger, concentration problems, and more vigor than control subjects. They also reported fewer symptoms of stress, including peripheral manifestations of stress (e.g., tingling in hands and feet), cardiopulmonary symptoms of arousal (e.g., racing heart, hyperventilation) central neurological symptoms (e.g., dizziness, faintness), gastrointestinal symptoms (e.g., upset stomach, diarrhea), habitual stress behavioral patterns (e.g., smoking, grinding teeth, overeating, insomnia), anxiety/fear, and emotional instability compared to those still waiting for the program. Results of a 6-month follow-up, including both experimental and wait-list participants who had by then completed the program, indicated a maintenance of these gains over the follow-up period.[103]

The next study conducted by our group was a pre–post MBSR intervention with early-stage breast and prostate cancer survivors who were all at least 3 months posttreatment. Outcomes included biological measures of immune, endocrine, and autonomic function in addition to similar psychological variables as previously.[104,105] Fifty-nine and 42 patients were assessed pre- and post-intervention, respectively. The 59 patients attended a median of eight of a possible nine sessions over the 8 weeks (range 1–9). They also practiced at home as instructed, reporting an average of 24 minutes/day of meditation and 13 minutes/day of yoga over the course of the 8 weeks. Significant improvements were seen in overall quality of life, symptoms of stress and sleep quality.

A unique modification on MBSR that has been applied to cancer patients is called mindfulness-based art therapy (MBAT), which combines the principles of MBSR with other creative modalities. In a recently completed 2-year RCT ($N =$ 111), researchers compared the 8-week MBAT intervention to wait-list control in a heterogeneous cohort of women with mixed cancer types receiving usual oncologic care. They found that compared to the usual care group, the MBAT participants had less depression, anxiety, somatic symptoms of stress, and less hostility.[106]

Other groups are also applying modifications of the MBSR program to cancer patients, and presenting psychological results at scientific meetings. For example, Bauer-Wu and Rosenbaum have adapted MBSR for individual use in isolated hospitalized bone-marrow transplant (BMT) patients[107] finding immediate effects on levels of pain and anxiety. Another group is investigating a shortened 4-session MBSR program for cancer patients.[108] Clinical work is ongoing, including through the Wellness Community (e.g., ref. 109), but no publications have yet resulted from these programs.

7.2. Sleep and Fatigue

Our recent work has focused on sleep problems in cancer patients, and how MBSR may be beneficial in treating this common problem in cancer patients. Similar to what others have reported, we found a very high proportion of our cancer patients with disordered sleep (approx. 85%) in a sample of 63 patients attending the

MBSR program. In these patients, sleep disturbance was closely associated with levels of self-reported stress and mood disturbance, and when stress symptoms declined over the course of the MBSR program, sleep also improved.[110] Improvements were seen on the Pittsburgh Sleep Quality Index subscales of subjective sleep quality, sleep efficiency, and hours of sleep. On average, sleep hours increased by ½ to 1 hour per night. This is similar to our previous results, where sleep was measured using a less refined scale. Nonetheless the proportion of patients who reported their sleep as "good" improved from 40% before the program to 80% afterwards,[111] reinforcing the more recent finding.

Reductions in fatigue had also been observed in our previous work, with scores on the Profile of Mood States subscales of vigor and fatigue both changing in favorable directions after the MBSR program.[103] In the sleep study mentioned above, fatigue scores were also measured by a POMS subscale.[110] The change in fatigue scores was statistically significant, and associations were found between fatigue and sleep at both pre- and post-intervention, such that more sleep difficulty was associated with greater fatigue. However, a statistically significant relationship was not found between improvements in fatigue and sleep, rather between changes in symptoms of stress and fatigue, and between changes in mood disturbance and fatigue. Therefore, it may be that as patients began to sleep better, they also became less stressed and moody, and subsequently became less tired and had more energy—a hypothesis that remains to be tested.

A study by Shapiro *et al.*[112] also examined the relationship between participation in an MBSR program and sleep quality and efficiency in a breast-cancer population. They did not find statistically significant relationships between participation in an MBSR group and sleep quality; however, they did find that those who practiced more informal mindfulness reported feeling more rested.

7.3. Existential and Spiritual Outcomes

Our more recent work has evolved to investigate the effects of MBSR on the types of existential outcomes described in the introduction. One way of examining these personally meaningful outcomes is through patient self-assessment using questionnaires developed to measure constructs such as benefit-finding and spirituality. We assessed posttraumatic growth using the Post-Traumatic Growth Inventory (PTGI) and Spirituality using the Functional Assessment of Chronic Illness Therapy-Spiritual Well Being (FACIT-Sp) scale in 28 MBSR class participants with mixed cancer diagnoses an average of about 1.5 years since diagnosis, before and after program participation (paper under review). Stress-specific symptoms and mood disturbance were also assessed. Participants' scores on the spirituality measure improved significantly over time, while nonsignificant increases in posttraumatic growth were observed. Overall, improvements in symptoms of stress and mood disturbance, depression and anger, confirmed our previous findings within a new group of patients.

In order to investigate the phenomenon of enhanced spirituality and posttraumatic growth in greater depth, we chose to conduct qualitative interview research with a specific subgroup of our MBSR participants.[122] Nine cancer patients who had participated in the 8-week MBSR program, and who continued to attend weekly drop-in MBSR sessions, which consist of meditation and yoga practice, were interviewed for this study. Qualitative research was conducted using a grounded theory model. Participants were between 43 and 77 years in age (average age 60.8 years). Additionally, participants had been active in the drop-in group for between 1 and

6 years (average time 2.8 years). Of the nine participants, four had breast cancer, two had prostate cancer, one had ovarian cancer, one had a malignant melanoma, and one had multiple cancers (lung, thyroid, and Hodgkin's disease). Participants had been first diagnosed between 31 years (with a recent recurrence) and 4 years previously (median, 5 years), and were well into survivorship mode.

Within semistructured interviews and a focus group, patients were invited to describe how adding meditation to their lives had affected them. Through analysis of the transcripts, five major themes were identified, labeled as: (1) Opening to change; 2) Self-control; 3) Shared experience; 4) Personal growth; and; 5) Spirituality. This information was used to develop specific theory concerning mechanisms whereby MBSR effects change for cancer patients. In this theory the initial participation in the 8-week program is seen as only the beginning of an ongoing process of self-discovery, a slight shift in orientation that begins the growth process. At that time patients feel isolated, scared and unsure of what to do in the face of a cancer diagnosis. The MBSR program helps to meet their needs for understanding they are not alone in their journey, teaches concrete tools for self-regulation, and introduces ways to look at the world they may not have previously considered. This results in benefits such as reduced stress symptoms and lower levels of mood disturbance.

As practice progresses in the drop-in group, social support deepens as relationships are further developed, and people begin to learn to be less reactive and exercise more diffuse self-regulation across a wider variety of life circumstances. Underlying this process is a theme of personal transformation, of feeling part of a larger whole. With this comes the development of positive qualities of personal growth and positive health, beyond merely the symptom reduction documented over the course of the initial program. A growing spirituality of finding meaning and purpose in one's life and feeling increasingly interconnected with others is part of this personal transformation. Qualities of gratitude, compassion, and equanimity may be the ultimate culmination of practice—very similar, in fact, to the goals of many of the Eastern practices upon which MBSR is based. Although this theory of the development of mindfulness practice is stated in linear terms, all of these processes likely occur simultaneously to varying degrees. Accordingly, the emphasis or importance of different aspects may oscillate depending on the life circumstances of each individual.

7.4. Biological Outcomes

We have also become interested in the effects of MBSR on some of the biological processes identified by researchers as affected by cancer treatments, which may have potential consequences in terms of future health and disease recurrence. In the study described above with breast and prostate survivors an average of 1.1 years post-treatment, we investigated immune function by looking at the counts of a number of lymphocyte subsets, including T cells (divided into helper and cytotoxic T cells) and NK cells. In addition to counting cells, we also tested their function by measuring how much of four different cytokines were secreted by the T and NK cells in response to an immune challenge. Cytokines were either of the pro-inflammatory or anti-inflammatory variety—pro-inflammatory processes have been associated with several poorer outcomes in both cardiovascular and cancer patients.[100,113] Although there were no significant changes in the overall number of lymphocytes or cell subsets, T-cell production of interleukin (IL)-4 increased and interferon gamma (IFN-λ) decreased, whereas NK cell production of IL-10 decreased. These results are consistent with a shift in immune profile from one associated with depressive symptoms to a more normal profile. We also assessed the patterns of change over a full year following program participation. Although complicated, the pattern of change in cytokines over 1 year of follow-up supported a continued reduction in pro-inflammatory cytokines.[114]

We also looked at salivary cortisol levels, since daily salivary cortisol levels have been related to stress and health, and are often dysregulated in cancer survivors; such dysregulation has been associated with poorer disease outcomes. We assessed salivary cortisol three times daily both before and after program participation, and looked at the shape of the pattern of cortisol secretion throughout the day—abnormal profiles have been associated with shorter survival in metastatic breast cancer patients.[115] Interestingly, these hormone profiles also shifted pre- to post-intervention in our participants, with fewer evening cortisol elevations found post-MBSR and some normalization of abnormal diurnal salivary cortisol profiles occurring.[104] The clinical significance of this finding has yet to be pursed. We then followed these same participants for a full year, and found continuing decreases in overall cortisol levels over 6 and 12 months of follow-up, mostly due to decreases in evening cortisol levels.[114] This is significant as higher cortisol levels, particularly in the evening, are considered to be an indicator of dysregulated cortisol secretion patters and poorer clinical outcomes.

Measures of autonomic system function have also been of interest, since cancer survivors are at high risk for cardiovascular disease. Hence, we looked at the effects of MBSR on resting blood pressure and heart rate. In a group of breast and prostate cancer survivors, overall resting systolic blood pressure (SBP) decreased significantly from pre- to post-MBSR.[114] Correlations were significant between resting HR and mood disturbance scores at pre-intervention, and between HR and the total stress scores at pre-intervention, and 6- and 12-month follow-ups. This indicates that elevated resting HR was related to the experience of more symptoms of mood disturbance of stress. Consistently, elevated HR is also a risk factor for cardiovascular disease.

In other work with biological outcomes, an innovative study by Kabat-Zinn's group looked at the effects of combining a dietary intervention with MBSR on prostate specific antigen (PSA) levels, an indicator of the level of activity of the prostate cancer, in men with biochemically recurrent prostate cancer.[116] They found the combined program resulted in a slowing of the rate of PSA increase in a pilot sample of 10 men, and are currently conducting a larger RCT to verify this significant impact on such an important marker of biochemical recurrence in prostate cancer.

Taken together, these studies begin to hint at the potential for psychosocial interventions, specifically MBSR, to impact biological mechanisms that may be important for future health outcomes. This research area is in its infancy and many opportunities for innovative research exist.

8.0. FUTURE DIRECTIONS

The intention of this review was to provide an overview of several stress-management approaches; focusing more closely on the details of the one we are most familiar with, MBSR. It should be clear that there are a number of effective approaches to reducing stress and addressing common problems of cancer survivors, but MBSR appears to provide an approach that is relatively easy to learn and use, that has potential to impact important outcomes for cancer survivors across a number of interconnected domains. Since the research on MBSR in cancer survivors is still in its infancy, there are many untapped avenues of research and many questions that remain unanswered.

One valuable line of inquiry is investigating potential mechanisms of MBSR action. As indicated in Figure 1, a number of psychological mechanisms have been proposed[88] including "Reperceiving," which denotes a fundamental shift in perspective. Through the application of mindfulness, one is able to stop or refrain from identifying oneself with the contents of consciousness (i.e., one's thoughts), and view moment-by-moment experience with greater clarity and objectivity. Rather than being immersed in the drama of one's personal narrative or life story, one becomes able to stand back and simply witness it. This is hypothesized to lead to additional mechanisms that in turn contribute to the positive outcomes produced by mindfulness practice: (1) self-regulation and self-management; (2) emotional, cognitive, and behavioral flexibility; (3) values clarification; and (4) exposure. Inherent in all of these mechanisms are the three axioms of intention, attention, and attitude. The process by which these mechanisms go on to effect other outcomes such as quality of life and well-being, and whether changes do indeed happen through the process of Reperceiving, has not been empirically tested. Indeed, measures for assessing Reperceiving and the other mechanisms have not yet been developed or validated in many cases.

Another question of a more practical nature is how to improve access to MBSR programs. Currently, programs are offered in face to face groups in select communities (usually larger cities), leaving survivors in more remote areas without access. One possibility is that the Internet or videoconferencing could be used as a medium to deliver MBSR or other stress-reduction programming. A home study program with CDs could also be developed for use online, and evaluated in a similar manner as face to face group formats. Telehealth could be applied to program delivery, with participants in several remote sites joining program leaders by videoconference in a different location for the group. Modifications of program length and home practice times are also areas of interest that have not yet been seriously studied.

In terms of evaluating MBSR more rigorously, clinical trials with active control groups should be conducted. Thus far, MBSR has been compared primarily to usual care or wait-list, but not to active control groups such as CBSM or SEGT. Randomized clinical trials directly comparing standardized, empirically supported treatments in cancer survivors would move a step beyond demonstrations of efficacy comparing MBSR to usual care, and represent a much more difficult test. It would likely be the case that some individuals would excel in one format but not others, so pinpointing the characteristics of those who best respond to each type of intervention will be important, from the perspective of individually tailoring each survivor's personal recovery plan.

Other areas of investigation of biological outcomes could include assessing genetic markers of response to treatment, similar to approaches used to tailor drug treatments to individual patients. Because the relevance of traditional immune measures such as lymphocyte counts and cytokine production is unclear in cancer progression, outcomes more directly relevant to cancer could also be assessed, such as tumor growth factors and anti-angiogenesis markers.[113]

Finally, there is a growing interest in the economic and functional impact of psychosocial treatments for cancer survivors in areas such as lost productivity and return to work.[117,118] Functional outcomes such as the ability to perform activities of daily living and effects of interventions on factors such as fatigue and quality of life are important areas to investigate. The economic cost of ongoing limitations in cancer survivors is also important. We showed in one study that total direct costs to the health care system in women recovering from breast cancer randomly assigned to a 6-week psychoeducational intervention were fully 25% less over the subsequent 2-year period than those of comparable women randomized to usual care.[119] This is a striking example of the potential benefit of psychosocial interventions in dollars and cents terms, but little other research has been conducted in this area (see ref. 120 for a review). Economic research needs to become more sophisticated to consider not only direct medical costs, but also societal costs of lost productivity in cancer survivors, and how stress-reduction interventions may help to mitigate such losses.[121]

In summary, there are many unanswered questions and research opportunities relating to MBSR and stress-reduction research in cancer survivors. Our research program and others throughout the world investigating stress-reducing interventions in cancer survivors have provided a basis for understanding some of the 'basic effects of these approaches. Future research is now poised to move beyond these rudiments. The ultimate goal of this research is to offer more meaningful options for the growing cohort of survivors searching for ways to live a better life after cancer.

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Chapter 20

Pain and Function

A Psychosocial Perspective

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1.0. PAIN AND DISABILITY: A PSYCHOSOCIAL PERSPECTIVE

Little is currently known about the psychology of pain among cancer survivors. While numerous investigations have addressed the psychological correlates of the cancer experience, the focus of previous research has been on understanding and lessening the suffering of the cancer patient while undergoing treatment or at the end of life. Questions concerning the impact of pain on the emotional, social, and occupational functioning of the cancer survivor remain largely unexplored.

Advances in cancer treatment have had a significant impact on survival rates.[1] Continued advance in cancer care is expected to contribute to a growing population of cancer survivors. Research suggests that at least one of every three cancer survivors will continue to experience symptoms of pain.[2] Current treatment options for pain in cancer survivors are limited and of modest efficacy.[2–4] The problem is further complicated by the fact that pain symptoms are often viewed as secondary to the control of disease, and as such, frequently under-treated.[5,6]

The objective of this chapter is to examine the psychosocial determinants and impact of pain in cancer survivors. A biopsychosocial conceptualization of pain will be adopted in an effort to fully appreciate the multidimensional nature of pain experience. Available research will be summarized and avenues for future research will be explored. Finally, issues concerning the intervention needs of the cancer survivor will be discussed.

2.0. A BIOPSYCHOSOCIAL PERSPECTIVE ON THE PAIN EXPERIENCE OF CANCER SURVIVORS

Pain symptoms in cancer survivors can arise from multiple causes including adverse effects of cancer treatment, infection, and musculoskeletal problems (see Chapter 9).[7–10] Research suggests that 30–60% of individuals with cancer will continue to experience pain symptoms that will persist in the posttreatment period.[2,11–17] Neuropathic pain and somatic pain conditions are the most common pain diagnoses in cancer survivors.[18–20]

Compared to other domains of pain research, the psychosocial dimensions of pain in cancer survivors have received little attention. While issues related to the emotional impact of cancer pain have been researched to some extent, questions concerning the relation between pain and functional limitations in cancer survivors, or the psychosocial risk factors for pain and disability in cancer survivors have not been systematically investigated.[6,21–23]

Considerable research has accumulated over the past two decades indicating that medical status variables cannot fully account for presenting symptoms of pain and the functional limitations associated with health conditions.[24] Biopsychosocial models have been put forward suggesting that a complete understanding of pain experience and pain-related outcomes will require consideration of physical, psychological, and social factors.[22,25–27] Emerging research has supported the view that psychological factors play a significant role in the experience of pain and pain-related outcomes associated with cancer.[22,28,29]

3.0. THE IMPACT OF PAIN ON EMOTIONAL FUNCTIONING OF THE CANCER SURVIVOR

Of all mental health outcomes associated with persistent pain, depression is by far the most prevalent. Community surveys indicate that approximately 20% of individuals with persistent pain symptoms suffer from a diagnosable depressive condition.[30] Much higher rates are seen in specialty pain treatment centers.[31,32] There is considerable research indicating that prevalence rates of depressive disorders are higher in cancer patients than in the general population.[27,33,34] However, no research has yet to examine prevalence rates of depressive disorders in cancer survivors with persistent pain.

Cancer pain can exert a significant negative impact on emotional functioning.[35,36] Higher levels of pain have been associated with reductions in quality of life in long-term cancer survivors.[28,37,38] Higher levels of pain have also been associated with more severe depressive symptoms in cancer survivors.[39–41] Zaza and Baine[42]reviewed 19 studies that examined the association between cancer pain and psychological distress. The majority of studies reviewed (14 of 19) revealed a significant association between cancer pain and emotional outcomes such as anxiety, fear, and depression.[42]

Research in this area has appealed primarily to “diathesis-stress” formulations in efforts to explain how depression might arise following the development of a pain condition.[43] Diathesis-stress formulations essentially attempt to explain why some individuals become depressed as a function of their pain experience while others do not.[44] These models suggest that depressive symptoms might arise when vulnerability (or resilience) factors (i.e., diatheses) interact with vulnerability-relevant

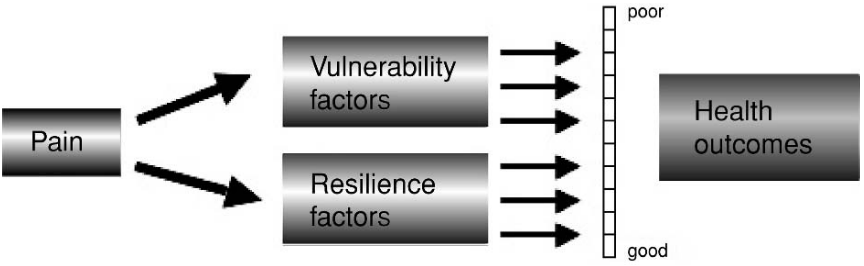

Figure 1. A Diathesis-Stress Model of Health Outcomes Associated with Pain.

contextual factors (i.e., stressors). As shown in Figure 1, diathesis-stress models are not specific to depression, but can be invoked to explain a variety of health outcomes.

Numerous investigations have addressed the role of pain catastrophizing as a determinant of depression and other pain-related outcomes.[45–47] Pain catastrophizing has been defined as "a negative cognitive set brought to bear during actual or anticipated pain experience."[48] Research has supported a multidimensional conceptualization of catastrophizing, comprising elements of rumination ("I can't stop thinking about how much it hurts"), magnification ("I'm afraid that something serious might happen"), and helplessness ("There is nothing I can do to reduce the intensity of the pain").

Prior to its emergence in the pain literature, catastrophizing had been discussed primarily within the context of cognitive theories of depression. For example, in Beck's[49] cognitive model of emotional disorders, catastrophizing is viewed as a "cognitive distortion" that might contribute to the precipitation and maintenance of depressive symptoms. Beck *et al.*[49] proposed that "depressive schema" might become activated following the occurrence of negative life events. Once activated, depressive schema were said to give rise to a variety of cognitive distortions including catastrophizing, overgeneralization, personalization, and selective abstraction. In Beck *et al.*'s[49] model, cognitive errors are expected to bias information processing in such a manner as to increase the likelihood of the development of depressive symptoms. Adapted to pain, a diathesis-stress model of depression would suggest that the events associated with the onset of pain, or the stressors associated with living with a persistent pain condition might contribute to the activation of depressive schema in vulnerable individuals.[43]

Bishop and Ward[50] examined the relation between pain catastrophizing and various pain-related outcomes in a sample of women who had been diagnosed with breast cancer. On average, women had been diagnosed 5 years earlier, and had been experiencing pain for approximately 18 months. Regression analyses revealed that pain catastrophizing contributed significant unique variance to the prediction of depression and anxiety, even when controlling for other types of coping strategies. In other words, of all the coping strategies assessed, pain catastrophizing emerged as the most important predictor of anxiety and depression.

There are indications that catastrophizing might contribute to a propensity to appraise pain symptoms as a sign of disease progression. Research suggests that 10–50% of cancer survivors attribute their pain to disease progression even when in remission.[15,51,52] A recent study reported that cancer survivors with high levels of pain catastrophizing were more likely to interpret increasing pain as sign of disease progression than cancer survivors with low levels of pain catastrophizing.[52] While cancer survivors tended to attribute their pain as a sign of disease progression, patients with rheumatoid arthritis tended to attribute their pain to exertion. The propensity to interpret pain signals as a sign of disease progression might lead to various adverse emotional outcomes such as depression, anxiety, and fear.[53]

In other domains of pain research, investigations have highlighted the potential contribution of a number of additional cognitive variables to the development or maintenance of depression. Appraisal-related variables such as perceived lack of control,[53] perceived limitations,[54,55] perceived interference due to pain,[56,57] perceived inadequacy of problem-solving skills,[58,59] and cognitive distortions[60,61] have been associated with elevations of depressive symptomatology in patients with persistent pain.

The results of numerous investigations suggest that self-efficacy for managing pain[54,62] might represent a protective or resilience factor against negative pain-related outcomes. In pain research, self-efficacy has been defined in terms of one's overall confidence in the ability to deal with symptoms, stresses or limitations associated with a pain condition.[63,64] Considerable research has addressed the relation between self-efficacy and pain-related outcomes in patients with arthritic conditions (e.g., rheumatoid arthritis, osteoarthritis, fibromyalgia).[28,65] High levels of self-efficacy are thought to impact on emotional functioning by promoting the use of coping strategies, increasing the range of activities individuals will undertake and by increasing the effort invested in activity.[66] The role of self-efficacy as a determinant of psychological and physical functioning in cancer survivors with persistent pain has yet to be systematically studied.

There is research to support relation between the use of pain coping strategies and pain-related outcomes in cancer survivors. Pain coping strategies are the various cognitive techniques or behaviors that individuals might use to manage the stresses associated with persistent pain.[46,67] In their efforts to cope with their pain, individuals might use "active" coping strategies such as problem-solving or distraction, or they might use "passive" coping strategies such as resting or activity avoidance.[68,69] Bishop and Ward[50] found that breast cancer survivors who used more active pain coping strategies also reported fewer depressive symptoms and fewer functional limitations due to pain.

There are indications that patients with cancer pain use fewer pain coping strategies than patients with chronic non-cancer pain. Dalton and Feuerstein[70] reported that, compared to chronic non-cancer pain patients, patients with cancer pain obtained lower scores on a measure of coping. Cancer pain patients also reported using more pain medication than chronic non-cancer pain patients. Cancer pain patients did not report more pain-related fears than chronic non-cancer pain patients.[70]

Other investigators have commented that comparisons of pain experience between individuals with cancer pain and chronic non-cancer pain reveal more similarities than differences.[71] The results of investigations showing similarities in the pain experience of cancer survivors and patients with non-cancer pain conditions suggest that interventions that have benefited individuals with non-cancer pain might also benefit the cancer survivor with pain.[28,71]

There has been growing interest in the relation between acceptance and adjustment to persistent pain.[72] McCracken and his colleagues have discussed acceptance as protective or resilience factor that might decrease susceptibility to depression in individuals with persistent pain.[73] In this context, acceptance has been defined as "an active willingness to engage in meaningful activities in life regardless of the experience of pain-related sensations, thoughts, and related feelings that might otherwise hinder such engagement."[73] In one study, higher scores on a measure of acceptance were associated with fewer depressive symptoms and lower levels of psychosocial and physical disability.[74] The degree to which acceptance contributes to resilience to depression or other pain-related outcomes in cancer survivors has yet to be systematically investigated.

The "vulnerability-relevant contextual factors" component of a diathesis-stress model of pain in cancer survivors would encompass all the stresses that might be associated with pain including persistent physical distress, treatment experiences, treatment phase, loss of employment, loss of financial security, loss of independence, disrupted family relation, etc.[38,75–77] In the bulk of research conducted to date on the health and behavioral health outcomes associated with pain, the presence of "vulnerability-relevant contextual factors" has been assumed more than it has been measured and there have been few tests of the hypothesized interaction between vulnerability factors and vulnerability-relevant contextual factors.[43,78]

Fatigue may represent an important vulnerability-relevant contextual factor in cancer survivors with persistent pain. It has been noted that symptoms of pain, fatigue, and depression appear to cluster in cancer survivors.[79] It has been suggested that the nature, severity, and impact of fatigue on the life of the cancer survivor is not well understood.[79,80] Fatigue overlaps to some degree with depression, and might be misattributed to a depressive state. Given that the task of coping with cancer pain is resource demanding, the cancer survivor with significant symptoms of fatigue might be particularly vulnerable to the adverse effects of persistent pain on mood and quality of life. Fatigue may interfere with the ability to participate in social and recreational activities that might otherwise act as a buffer to the stress and strain of living with pain. Clinical researchers have called for greater attention to the study of development and trajectory of fatigue symptoms associated with cancer pain.[79]

4.0. THE TREATMENT OF DEPRESSION ASSOCIATED WITH PAIN IN CANCER SURVIVORS

Research to date highlights several important aspects of depression associated with chronic pain in cancer survivors.[27,81] Depression not only impacts negatively on the quality of life of the individual suffering from persistent pain, but there are indications that depression adds to the burden of impairment associated with persistent pain.[33,81]

There is accumulating evidence that interventions that aim to reduce pain catastrophizing are associated with improvement in depressive symptoms.[82,83] Reductions in the helplessness dimension of pain catastrophizing appear to contribute most strongly to reductions in depression.[82] Intervention programs that specifically target catastrophic thinking in cancer survivors with pain may be the ones associated with the best outcomes.[84] There are indications that cognitive–behavioral interventions for cancer survivors not only reduce emotional distress but yields meaningful improvement in immune function as well.[85]

Unfortunately, depressive symptoms are frequently under-treated in patients with persistent pain conditions.[86] Clinicians will undoubtedly have noted that while a significant proportion of pain patients referred to their clinics have been prescribed antidepressant medication, only a minority of patients will be taking antidepressant medication at a dose level likely to ameliorate depressive symptoms.[85] One of the reasons for the under-prescription of therapeutic doses of antidepressants for depression associated with pain is that depression often goes undetected in primary care practice.[33] Patients will not necessarily report depressive symptoms to their physicians, and physicians may not enquire about mental health symptoms. Alternately, physicians may infer that depressive symptoms are a consequence of pain that will be alleviated once the pain has been effectively managed. The unfortunate consequence of both scenarios is that the patient does not receive the treatment that he or she needs.[86]

If has oft been noted that pain patients appear to be particularly sensitive to the side effects of antidepressant medication.[33,87] This view is expressed with sufficient frequency in clinical discussions giving the impression that side-effect sensitivity has been extensively studied in chronic pain. However, a search of the available literature provides little concrete evidence to clarify the relation, if any, between persistent pain and exaggerated reactivity to medication side effects. Clearly, this is an area that requires further investigation.

An early review of the literature on the treatment of depression in chronic pain suggested that treatment response to tricyclic antidepressants appeared to be similar in individuals with chronic pain and without chronic pain.[86] This statement however was based on only two controlled trials of antidepressant (tricyclic) medication for the treatment of depression in patients with persistent pain. Recent reviews reveal that there have not been any new controlled clinical trials of new generation antidepressant medication (e.g., SSRIs, tetracyclics) for depressed patients with persistent pain since 1991.[88,89]

The lack of research on the efficacy of pharmacological and psychological interventions for the treatment of depression associated with pain in cancer survivors is problematic. Questions concerning the relative efficacy of depression-specific interventions for cancer survivors with persistent pain need to be addressed in order to guide treatment decisions. In addition, there is little or no information available about the influence of drug interactions, particularly opioids, on the efficacy of depression-specific interventions for depressed cancer survivors with persistent pain. Given that persistent pain and depression are both associated with activity withdrawal (in other pain conditions), the depressed cancer survivor with persistent pain may benefit most from multidisciplinary approaches that combine pharmacotherapy, depression management strategies, and activity mobilization strategies.[83]

5.0. THE SOCIAL CONTEXT OF PAIN IN CANCER SURVIVORS

There have been numerous anecdotal discussions of important social contextual influences on the experience of emotional distress, pain, and functional limitations in cancer survivors. A physician with cancer, Mullan[90] likened the experience of cancer to seasons of the year. He described the first season as the period extending from diagnosis to the termination of initial treatment. According to Mullan,[90] this period was dominated by treatment and treatment side effects. The second season began with the termination of initial treatment and was dominated by watchful waiting, and regular follow examinations. The third season, survival, emerged as the symptom-free period extended over time. The fourth season involved symptom recurrence.

It is likely that the pain experience of the cancer survivor varies as a function of the "season" of cancer that he or she is living.[91] During treatment, pain symptoms may be tolerated as a necessary consequence of the potentially life saving effort. Pain treatment may be viewed as secondary to treatments aimed at saving the individual's life. The second season might present particular challenges. Pain is likely to be a central player during the watchful waiting period. The cancer survivor might be alert to changes in the location or intensity of pain; with each change possibly signaling the return of cancer.[22] During the third season, mild pain symptoms might have significant impact on mood or disability if accompanied by fear of return of symptoms.[91] In the context of recurrence of cancer, pain symptoms might add to the burden of stress and strain of disappointment, anxiety, and the re-instatement of a gruelling treatment regimen.[22]

Mechanic and his colleagues[92,93] discussed the change in role expectancies that accompanies the onset of illness. According to Mechanic,[92] during periods of active disease and treatment, individuals are relieved of a variety of life responsibilities such as domestic and occupational duties. The patient is expected to follow directives of treating professionals in order to maximize the probability of successful recovery. The social environment is expected to adopt a supportive and caregiving role in order to promote the recovery of the patient. In other words, there are implicit guidelines for the responsibilities of the patient and the caregiver. Following recovery, there is the expectation that the patient will begin to resume pre-illness responsibilities and the social environment will be absolved of further caregiving activities.

As in other illnesses, the cancer patient is likely relieved of domestic and occupational responsibilities and the social environment provides support and care. As the cancer-free period extends over time, there will be increasing call for the resumption of activities. This transition to the resumption of pre-cancer life role activities is likely to be determined by numerous social contextual factors. Pain symptoms are likely to play a role in the degree to which life role responsibilities are resumed. Depressive symptoms when present will add to the burden of disability and further impede life role resumption. Factors external to the individual might also play a role. Family support (or lack thereof) might impact on the degree to which pre-cancer responsibilities are resumed. In other domains of chronic pain research, it has been shown that patients with solicitous partners are more likely to display high levels of pain-related functional limitations than patients with partners who are not solicitous.[94,95] Workplace factors such as the availability of workplace modifications, supervisor–employee relations, and co-worker attitudes toward disability can be significant determinants of the probability that an individual with pain-related limitations will make a successful transition back to the workplace.[96]

6.0. PSYCHOSOCIAL INFLUENCES ON PAIN-RELATED LIMITATIONS IN CANCER SURVIVORS

Many individuals either discontinue or avoid activities that are associated with pain.[97,98] These might include activities of daily living, social and recreational activities, or occupational activities.[23] Research suggests that 15–20% of individuals with chronic musculoskeletal pain conditions will become permanently occupationally disabled.[99,100]

Few research investigations have addressed the nature or severity of functional limitations due to pain in cancer survivors.[17,23,101] It is possible that the prevalence of pain-related disability in cancer survivors might be comparable to that observed in other pain conditions.[97,102] In the study by Bishop and Warr,[50] only one third of breast cancer survivors were employed outside the home; 20% were receiving disability benefits. Little is currently known about the degree to which pain accounts for reduced occupational involvement of cancer survivors. Changes in life priorities, or other symptoms such as fatigue might also contribute to reduced occupational involvement.

Although pain has typically been considered the primary determinant of functional limitations in chronic pain sufferers, it has also been suggested that pain and disability are distinct and partially independent phenomena.[99,103] Research suggests that, in chronic pain patients, pain intensity rarely accounts for more that 10% of the variance in the severity of functional limitations.[97] Although the relation between pain and functional limitations has yet to be examined in cancer survivors, Sullivan *et al.*[98] reported that pain symptoms accounted for only 9% of the variance in self-rated functional limitations in a sample of mixed neuropathic pain patients. In recent years, increasing attention has been devoted to assessing the degree to which psychosocial factors might contribute to heightened risk for prolonged pain-related functional limitations.

Numerous investigations have been conducted addressing the role of psychosocial factors in the prediction of prolonged pain and disability associated with work-related musculoskeletal conditions.[26,104,105] Systematic reviews of prospective cohort studies indicate that initial levels of pain severity are predictive of prolonged pain-related disability.[106] Gheldolf *et al.*[107] found that pain-related fears were significant determinants of the inability to work in individuals with back pain. Cross-sectional and prospective studies have shown that high levels of pain catastrophizing are associated with more intense pain, more severe functional limitations, and more prolonged work absence.[108–110] Lack of confidence in the ability to perform physical activities has been associated with more severe functional limitations.[62,111] Pain severity and depressive symptoms have been associated with premature termination of involvement in pain management programs, with greater occupational disability, and have been implicated as factors contributing to the transition from acute to chronic pain.[86,112–114] On the basis of this research, variables such as pain catastrophizing, pain-related fears (i.e., fear of movement/re-injury), self-efficacy, outcome expectancies, and depression have come to be construed as psychosocial risk factors for chronic pain and disability.[104,115,116] Future research should examine whether psychosocial risk factors for pain-related disability identified in other pain conditions also predict pain-related disability in cancer survivors.

Table 1 provides a selective list of potential psychosocial risk factors for prolonged pain and disability in cancer survivors and the instruments commonly used to assess them.[117–129] It is important to note that these scales were not specifically developed for use with cancer survivors and therefore reliability and validity of these scales with cancer survivors must be investigated rather than assumed.

Only recently has research begun to investigate risk factors for pain and functional limitations in cancer survivors. Presurgical pain severity has been shown to predict the development of chronic pain symptoms in women treated for breast cancer.[130,131] Presurgical pain has been shown to contribute to acute pain following surgery and to acute and chronic phantom breast syndrome in women treated for breast cancer.[132,133] Presurgical emotional distress has also been shown to predict postsurgical acute pain in women with breast cancer.[134]

Table 1. Measurement Instruments for Psychosocial Risk Factors for Pain and Disability

Risk factor	Measure	Reference
Catastrophizing	Pain Catastrophizing Scale	Sullivan *et al.*[117]
Pain-related fears	Tampa Scale for Kinesiophobia	Kori *et al.*[118]
	Fear-Avoidance Beliefs Questionnaire	Waddell *et al.*[119]
Depression	Beck Depression Inventory II	Beck *et al.*[120]
	Centre for Epidemiological Studies Scale for Depression	Radloff[121]
Anxiety	State-Trait Anxiety Inventory	Spielberger *et al.*[122]
	Pain Anxiety Symptom Scale	McCracken[123]
Self-efficacy	Chronic Pain Self-Efficacy Scale	Anderson *et al.*[124]
	The Functional Self-Efficacy Scale	Barry *et al.*[64]
Coping	Coping Strategies Questionnaires	Rosenstiel and Keefe[46]
	Multidimensional Pain Inventory	Kerns *et al.*[125]
	Vanderbilt Pain Management Inventory	Brown and Nicassio[68]
Perceived limitations/ Pain beliefs	Pain Disability Index	Pollard[126]
	Survey of Pain Attitudes	Jensen *et al.*[127]
Person-Environment factors	Biobehavioral Pain Profile	Dalton *et al.*[53]
Pain Severity	McGill Pain Questionnaire	Melzack[128]
	Neuropathic Pain Scale	Galer and Jensen[129]

Pain severity in cancer survivors might impact on function by interfering with an individual's ability to attend or concentrate on a particular task to the degree required for successful completion.[135] Numerous investigations have shown that pain engages attention and interrupts current cognitive activity.[136] The attentional disruption effects of pain are greatest when the pain is novel, and unpredictable.[137,138] For the cancer survivor who experiences intermittent or persistent pain, negative effects of pain on attention might have a deleterious impact on his or her ability to perform social, recreational or occupational tasks. The relation between pain and compromised attentional processing in cancer survivors with pain should be investigated in future research.

Emotional arousal states such as anxiety and fear, particularly when associated with pain, can have a marked negative impact on task-related attentional engagement.[136,139] Emotional distress has also been shown to impact negatively on individuals' ability to adequately perform cognitive tasks. Depressive symptoms can interfere with the processing of complex information.[140] Depressive symptoms can also compromise the engagement of motivational resources necessary to perform various physical or cognitive tasks.[141] The adequate management of emotional distress states might be a key component of success for treatment programs that aim to facilitate social, recreational, and occupational re-integration of the cancer survivor with pain.

Risk factor research with cancer survivors should lead to the development of screening tools for the identification of individuals at risk for problematic outcomes following cancer treatment. Individuals identified at risk might then be considered for targeted interventions that might prevent the development of persistent pain and disability following treatment. In the absence of knowledge about relevant prognostic factors for problematic outcomes, interventions specifically targeting prognostic factors cannot be developed as yet.[96]

7.0. THE TREATMENT OF PAIN AND PAIN-RELATED DISABILITY IN CANCER SURVIVOR WITH PERSISTENT PAIN

A number of pharmacological interventions for cancer pain and post-cancer pain have been described in the literature.[142] Different classes of medication such as over-the-counter analgesics, opioids, and anticonvulsant drugs have been shown to yield significant pain relief benefit, at least for a certain percentage of patients.[2,3] The medical management of pain in cancer survivors is described in more detail in Chapter 10.

However, there are indications that cancer survivors might not always take full advantage of the pain management options available to them.[143,144] Ward[145] described a number of factors that influence individuals' decisions about the type of pain management approaches they will consider for the treatment of their pain. Ward reported that patients' fears about side effects or addiction, or concerns that pain complaints might be negatively perceived by treating professionals interfered with the proper management of pain symptoms. It has been suggested that the provision of accurate information about pain management options, and education about the appropriate use of pain medication should be an integral component of the treatment of cancer survivors.[143–146]

Concerns about side effects of pain medication might be particularly pertinent to the cancer survivor who wishes to resume pre-cancer role responsibilities. Certain medications used in the management of pain, such as some forms of antidepressants, can lead to excessive morning fatigue, dry mouth, nausea, and lethargy. Other medications, such as opioids, can result in mental clouding, and impaired coordination that can interfere with the adequate or safe performance of many activities of daily living. Although many side effects of pain medication dissipate in time, some individuals will continue to experience medication side effects of significant severity even after extended use. The cost-benefit analysis of balancing the pain reduction with the adverse side effects of medication might present particular challenges for the cancer survivor with pain who wishes to resume occupational involvement.

Cognitive–behavioral approaches have dominated psychological intervention research on cancer pain management. Cognitive–behavioral perspectives proceed from the view that an individual's interpretation, evaluation and beliefs about their health condition, and their coping repertoire with respect to pain and disability will impact on the degree of emotional and physical disability that will be associated with cancer.[25,28] It is important to note that the term cognitive–behavioral does not refer to a specific intervention but, rather, to a class of intervention strategies. The strategies included under the heading of cognitive–behavioral interventions vary widely and may include self-instruction (e.g., motivational self-talk), relaxation or biofeedback, developing coping strategies (e.g., distraction, imagery), increasing assertiveness, minimizing negative or self-defeating thoughts, changing maladaptive beliefs about pain, and goal setting.[67] A client referred for cognitive–behavioral intervention may be exposed to varying selections of these strategies.

In the early years of psychosocial oncology, numerous investigations assessed the effectiveness of cognitive–behavioral techniques to minimize the negative impact of aversive cancer treatment interventions.[147,148] Education has been a key feature of many interventions aimed at assisting individuals cope with aversive effects of cancer treatment or persistent pain following treatment.[144,145,149] Educational approaches have been used to increase individuals' understanding about pain symptoms, minimizing barriers to accessing options for pain treatment, and methods of managing the stresses associated with pain. Educational interventions have been offered as stand alone interventions, or in combination with interventions aimed at increasing the cancer survivors' ability to cope with pain symptoms.[28]

A number of cognitive–behavioral interventions have been developed to assist patients in coping with acute procedural pain that might be experienced during cancer treatment. For example, distraction strategies and imagery-based strategies have been used for the management of procedural pain in both children and adults.[147,148] Pain control strategies are typically taught prior to exposure to the painful procedure, and patients might then be coached through the procedure by a clinician. The results of several investigations suggest that these methods can be effective in reducing pain symptoms and emotional distress associated with painful cancer treatment.[150–152]

Albeit important intervention tools for acute procedural pain, strategies such as distraction, imagery, and hypnosis may have limited applicability for persistent pain. The high attentional resource demands of these strategies might interfere with a person's ability to engage in any other activity while utilizing the strategy. The attentional resource demands of these strategies also place limits on the duration of time that they can be invoked to deal with a pain episode. For the patient who must deal with pain symptoms throughout the day, for months or years, even though they may wax and wane, alternate approaches to pain management are needed.

Keefe *et al.*[153] described a three-session cognitive–behavioral, partner-assisted, pain-management intervention for terminally ill cancer patients. The program of intervention was developed on the basis of research with osteoarthritis patients showing that partner-assisted pain management improved the physical and emotional function of the pain patient as well as the emotional functioning of the spouse or caregiver.[153] The three-session program included (1) education about the nature of pain experience and different options for pain control, (2) instruction in the use of pain coping strategies, and (3) instruction in activity pacing. The intervention program was delivered by nurse educators. Patient and partner outcomes following participation in the partner-assisted intervention were compared to a usual care control group. Although there were no significant differences between groups on patient outcomes, there was a trend toward reduced pain and increased quality of life. The partners in the partner-assisted intervention showed significant increases of confidence in their ability to assist the patients in methods of pain control.[146] The authors suggested that the modest impact of the intervention on patient outcomes might have been due to the severity of physical and emotional distress experienced by the terminally ill patients. It is possible that this type of intervention, perhaps longer in duration, or combined with medication, might be useful for cancer survivors and their partners.

Few interventions have addressed the efficacy of pain management interventions for cancer survivors.[22,154] In a recent study, Dalton *et al.*[155] examined the effects of coping skills training on pain and distress of cancer survivors. In one group, patients received a standardized intervention program consisting of education, coping skills training, problem-solving, cognitive-restructuring, and relaxation. A second treatment condition consisted of similar elements but was customized to the patients' pain problem profile. Both treatment conditions yielded more positive pain-related outcomes than the control group.[155] Tailoring the intervention to the patient's pain profile led to more rapid improvement than the standardized intervention.

Clinical findings suggesting that pain contributes only modestly to disability, and that pain management programs yield only minimal change in pain levels have led many investigators to reconsider whether pain reduction should be the primary goal of psychological interventions for individuals with persistent pain.[96,156] Research suggests that programs that maximize activity involvement and resumption of key life roles are the ones most likely to be associated with return to pre-illness (or pre-injury) levels of functioning.[157–159]

As can be seen from the list of strategies included in cognitive–behavioral pain management programs, some are clearly linked to facilitating resumptions of life role activities (e.g., goal setting) while others are primarily palliative in nature (e.g., relaxation, imagery). In a related fashion, many cognitive–behavioral interventions have as their primary focus the reduction of emotional distress or the reduction of pain. While emotional distress and pain no doubt contribute to functional limitations, the reduction of emotional distress and pain are typically not sufficient to contribute in a meaningful manner to resumption of life role activities.[159] There are grounds to caution the use of overly palliative or passive psychological intervention strategies in the treatment of individuals with persistent pain when functional restoration is also a major goal. In other domains of practice, palliative or passive intervention strategies have been shown to accentuate as opposed to ameliorate pain-related disability.[97]

There have been a number of recent studies that have highlighted that the psychological predictors of pain are quite distinct from the psychological predictors of disability.[110,160] These findings suggest that if disability reduction is the goal of treatment, interventions will differ from those that would be considered if pain reduction was the goal of treatment.[161] Clearly, from a quality of life perspective, maximizing or restoring function in cancer survivors is of primary concern.

In recent years, a number of risk factor targeted interventions have been developed for the prevention of pain-related disability associated with musculoskeletal conditions.[162–164] These approaches differ from traditional psychosocial interventions for pain insofar as individuals are selected for treatment on the basis of psychosocial risk profiles, and interventions are designed to specifically target prognostic factors for pain-related disability. Research to date indicates that treatment-related reductions in psychological risk factors can yield significant improvement in pain severity, depression, and return to work.[115,162–165] Intervention approaches that target risk factors for disability associated with post-cancer pain might prove to be effective in restoring function, maximizing full social participation and increasing quality of life in cancer survivors.

8.0. FUTURE RESEARCH

As this review indicates, questions concerning the psychosocial dimensions of pain and function in cancer survivors have yet to find a place on the priority list of many research agendas. Although the magnitude of the pain problem in cancer survivors has been known for some time, basic questions about the nature and severity of functional limitations in cancer survivors with pain have yet to be addressed. Research describing the adverse impact of pain symptoms on the lives of cancer survivors will

Table 2. Building a Research Agenda: Priority Areas

1. Determining the prevalence of mental health problems in cancer survivors with pain.
2. Identification of vulnerability and resilience factors for depression in cancer survivors with pain.
3. The development and evaluation of interventions for the management of depression in cancer survivors with pain.
4. Examining the influence of opioids on the efficacy of interventions for depression in cancer survivors with pain.
5. Identification of vulnerability and resilience factors for functional limitations in cancer survivors with pain.
6. Development of screening measures for the detection of risk factors for pain and functional limitations in cancer survivors.
7. Investigating the role of fatigue as a determinant of health and behavioral health outcomes in cancer survivors with pain.
8. Investigating the effects of pain severity on attention and concentration in cancer survivors with pain.
9. Examining the determinants of decisions to discontinue employment in cancer survivors with pain.
10. Investigating the efficacy of interventions designed to reduce functional limitations and facilitate life role reintegration in cancer survivors with pain.

be required in order to mobilize the resources necessary to meet the treatment needs of this ever-growing population.

Research will also be required to identify the determinants of behavioral health outcomes and functional limitations in cancer survivors with pain. In the absence of this information, the development of intervention programs is likely to proceed with little empirical direction. In the interim, based on the literature addressing the psychological determinants of pain and pain-related disability in other domains of pain research, intervention strategies that aim to reduce helplessness and catastrophic thinking, increase perceived control and self-efficacy, and maximize resumption of important life role activities may contribute to more positive health and behavioral health outcomes for cancer survivors.[28,165,166] Table 2 provides a summary of priority research areas relevant to psychosocial factors associated with pain outcomes in cancer survivors.

Cancer survivors will continue to experience debilitating symptoms of pain following treatment that can impact on function. Once symptoms of pain become chronic, available methods of managing pain, whether pharmacological or psychological, have only modest impact on suffering and function. If individuals at risk for persistent post-cancer pain and those with high levels of pain-related disability can be identified before the problem becomes chronic, individuals' suffering might be prevented or reduced to a significant degree. There is an urgent need to develop a stronger research basis for the development of interventions aimed at preventing and managing the pain and its functional impact among cancer survivors with different types of cancers. Given the pending increase in the size of the cancer survivor population and the inherent morbidity and personal and societal costs associated with persistent pain following cancer treatment, increased knowledge of the determinants of post-cancer pain and disability will be important both for improving quality of life of patients and maximizing the overall cost-effectiveness of cancer treatment.

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Chapter 21

Work

Jos Verbeek and Evelien Spelten

1.0. INTRODUCTION

The situation of cancer patients returning to work has taken a turn for the better. Where early research reported profound job discrimination of cancer patients (e.g. Feldman[1]), recent literature suggests that breast cancer patients are only slightly less frequently unemployed than their healthy controls.[1] Maunsell *et al.* found a statistically significant 7% difference in risk of being unemployed between breast cancer survivors and healthy controls 3 years after diagnosis and concludes that job discrimination is not an issue anymore. In a more recent survey of return to work among breast cancer patients, only 7% perceived that they were discriminated against because of their cancer diagnosis.[2] However, this does by no means imply that the return to work process cannot be difficult for individual patients.[3] This could also be reflected in the finding that cancer is among the most frequent causes of dispute and litigation.[4]

Return to work has been a topic of interest in research for over 30 years, where nevertheless only a few attempts have been made to transfer knowledge to the field of cancer survivorship. In this chapter, we consider the main points that have been addressed in research. We look at the remarkable change in tone and issues, which has taken place over the course of the past 30 years. In this context, we present a model of factors impacting the return to work of cancer patients. We reflect on the progress that has been made and we realize that not all problems have been solved. Despite the obvious improvements, cancer patients still have to battle ignorance and hostility in the workplace and still have to cope with the aftermath of a diagnosis and treatment which has a significant impact upon their lives and well-being. We note areas and issues that will need future attention. Within this perspective we present the results of a prospective cohort study we conducted and look at the impact of fatigue on the return to work of patients.

Now that we realize that a cancer patient returning to work is no longer the exception, the next step should be taken. We need to consider how to make the patient's transition back to work as unproblematic as possible. The second half of this chapter will therefore focus on ways forward in aiding and supporting cancer patient in their return to work.

2.0. EXTENT OF THE PROBLEM

There is a substantial percentage of people below the age of 65, who see their lives affected by cancer. Advances in the detection and treatment of cancer, combined with an aging population, mean greater numbers of cancer survivors in the near future.[5] Not all cancer survivors are old. In fact, current estimates suggest that roughly 40% of the cancer survivors are working age adults.[6,7] This has increased attention for the societal reintegration of cancer patients. Despite the improving prospects, diagnosis and treatment still have such an impact on patients that often some form of societal reintegration is essential. The majority of the younger and middle-aged survivors will be part of the work force at the time of diagnosis. In the United States they accounted for about 4 million workers in 2002. Accurate estimates on the prevalence of cancer in the working population are hard to come by.[8] There is still a need for more systematic collection of data on the employment status of cancer patients. Still, irrespective of the possible size of the group, for this group return to work is an important aspect of societal reintegration.

3.0. IMPORTANCE OF WORK

Being able to return to work and to stay at work is important, both for society and for the individual. From a societal point of view it is important to reduce avoidable work incapacity. Economic loss is involved in unnecessary work cessation. From an individual's point of view, not being able to return to work following an illness frequently results in financial loss, social isolation, and reduced self-esteem. This financial loss is additional to the increased financial costs patients already endure due to their illness.

Conversely, return to work can improve the quality of life of cancer patients, can have a positive effect on self-esteem and social or family roles. Patients consider return to work to be important. Work performance after cancer treatment is frequently seen as a measure of recovery in its own right.[9]

4.0. LITERATURE REVIEW

Over the course of a more than 30-year period, studies have been conducted into the occupational rehabilitation of cancer patients and in issues relating to job discrimination. McKenna's report in 1973 can be seen as the formal start of interest in studies of job discrimination of cancer patients in the United States. In this report, McKenna describes the adverse work and insurance history of his patients.[10] These studies were followed by the extensive Feldman studies.[1] Feldman conducted a 5-year study of the work experiences of blue collar workers, white collar workers, and youths with cancer histories in the 1970s and reported job discrimination as well as factors impacting on the return to work of cancer patients. The results of these studies still serve as the basis for quotes on blue collar workers having problems returning to work due to the physical nature of their work. In addition, in 1989 Ivan Barofsky edited his book: *Work and Illness: The Cancer Patient*, one of the very few books on the subject. A relative void which is somewhat lessened by the book in hand.

In retrospect, it emerges that the United States dominated the first years of research, placing the spotlight on legal issue such as job discrimination and on insurance problems experienced by cancer patients. Major issues were: access denied to life insurance and health insurance, as well as blatant job discrimination. For example, affordable private health insurance is usually tied to a particular job.[11] These issues appear to be largely the result of the social security and legal system, or lack thereof in this country and thus describe a situation that is far from applicable across the globe.

There has been a steady flow of research on the occupational rehabilitation of cancer patients, mainly conducted in North America.[12,1,13,14] These studies have focused on the patient's perspective and have signaled that cancer survivors report problems upon their return to work. The main difficulties were health and life insurance problems and a lack of understanding from coworkers. Sometimes these problems led to survivors leaving the work force.[1,10]

In 2002, we published a literature review for the period 1985–99, thus covering roughly the second half of the total period of 30 years.[15] In this review we provided an overview of research into the return to work of cancer survivors. We examined both the rate of return to work and factors impacting this return. In order to know how many patients and which patients need help, not only information is required on the percentage of patients for whom return to work is relevant, but also on factors associated with return to work.

From our review, it became apparent that the earlier emphasis on legal and insurance issues had been augmented by a wider scope of factors impacting the return to work of cancer patients. Ranging from self-esteem, through the effects of chemotherapy to social support and lymphedema as well as fatigue and job context.

For a more systematic approach, the factors reviewed were categorized according to the World Health Organization (WHO) disability model into work-related, disease- or treatment-related, and person-related factors.[16] Health complaints, mood, and other psychological factors were categorized as person-related factors. Health complaints were subsumed under person-related factors, although health complaints can be related to the disease and treatment. Since all data were based on patients' reports and since complaint levels are known to show individual variation, this seemed a more appropriate categorization. The association with work-related, disease- or treatment-related, and person-related factors was considered in terms of a positive association (indicating facilitation of return to work), a negative association (implying a hindrance to return to work), or no association with return to work.

4.1. Work-Related Factors

A positive attitude of coworkers and discretion over work hours or amount of work was positively associated with return to work. Most work-related factors, however, were negatively associated with return to work, such as manual labor and work posing physical demands. Interestingly, discrimination at work was not significantly related to return to work and did not seem to be a more prevalent problem among cancer survivors than found in a control group of persons without cancer.[17] However, in a more recent survey women with breast cancer who perceived discrimination because of cancer were three times less likely to return to work than those who did not perceive discrimination.[2]

4.2. Disease- and Treatment-Related Factors

The only positive association was related to the number of months since the end of treatment. The chance of a return to work increased if more time had passed since the end of treatment. Most factors related to disease and treatment were not related to return to work. Mixed results were found for disease stage and cancer site. In a study of patients with Hodgkin's disease, as well as in a study of lymphoma patients, disease stage (divided in stages I–IV) was not related to return to work.[18,19] In a study of breast cancer patients, disease stage was coded as a three-level variable into 'local', 'regional', and 'remote'. Women diagnosed with regional and remote disease stage were more likely to be on leave 3 months after diagnosis than women diagnosed with localized disease.[20] Equally, in a study of patients with lung, cervical, pancreatic, and prostate cancer, a negative association between disease stage and return to work was found.[21] However, no further specification of disease stage was given in the latter study. Weis *et al.* studied a heterogeneous group of cancer patients and found that patients with head and neck cancer and breast cancer reported most problems upon their return to work.[22] Similarly, van der Wouden *et al.* reported more problems in returning to work for patients with head and neck cancer.[23] Patients with testicular cancer generally reported very few problems upon returning to work and consequently had a high rate of return to work. The relatively few problems in return to work of patients with testicular cancer were also reported in a study by Bloom *et al.*[24] In this study, patients with testicular cancer were compared to patients with Hodgkin's disease. The reporting of fewer problems by testicular cancer patients was considered to be related to their treatment having less consequences than in other cancer patients.

4.3. Person-Related Factors

Mobilizing social support was positively associated with return to work.[25] However, most person-related factors were negatively associated with return to work. For example, a changing attitude toward work reflected a reduced importance of work and a decrease in aspirations with regard to work. These changes were negatively related to return to work.[14] With the exception of increasing age, none of the sociodemographic characteristics were found to have a statistically significant relation with return to work. Mixed results were found for increasing age, fatigue, and reaction to diagnosis/treatment. For increasing age, three studies reported no relation and three studies reported a negative association with return to work. Equally, fatigue was found to have either a negative or insignificant relation. In a study of men with testicular cancer, the reaction to diagnosis/treatment was found to have both a positive and a negative relation. For some patients surviving the debilitating treatments made them perceive themselves as stronger and more capable. Other patients felt less confident about their physical ability in relation to their work, or about their ability to cope with stress. They also commented on becoming less interested in work achievements as a result of having cancer. "Life is too short" to be so involved with work.[26]

Although we recognize the need for additional corroboration of these findings, the accumulated results from the review suggest that:

- A supportive work environment facilitated return to work.
- Manual work or work which requires strong physical effort is negatively associated with return to work.
- With respect to disease and treatment related factors, patients with head and neck cancer, in particular, are at a disadvantage when returning to work, whereas patients with testicular cancer experienced relatively few problems upon their return to work.
- Sociodemographic characteristics, including education, income, gender, and marital status, were not found to be associated with return to work.
- Although it is generally assumed that increasing age is an important hindrance in return to work, results were mixed. Most studies did not find an association, while only one study reported a negative relation between increasing age and return to work. The results did not seem to be biased toward a younger group of workers with a relatively good prognosis.
- Moreover, all studies suffered from one or more of the following methodological weaknesses: the use of small samples, unstandardized, study-specific instruments, cross sectional rather than longitudinal designs, and no statistical testing of results.
- Finally, the rate of return to work in these studies varied from 30 to 93%, with a mean rate of 62%.

5.0. THE IMPACT OF FATIGUE AND OTHER CANCER-RELATED FACTORS ON RETURN TO WORK

In an attempt to overcome most of the methodological weaknesses discussed above, we conducted a longitudinal prospective cohort study into the return to work. The aim of the study was to assess the impact of fatigue and other cancer-related symptoms on the return to work of cancer survivors.[27] For this study we developed a model of the impact of cancer-related symptoms on the return to work of cancer patients, controlling for clinical factors, subject-related factors, and person-related factors (Figure 1).

Cancer is a collective name for a heterogeneous group of diagnoses whose treatment is far from uniform. There is some evidence that the consequences of the illness and its treatment, the cancer-related symptoms that are experienced by patients, can affect the likelihood of resumption to work. For example, the relatively rapid return to work of patients with testis carcinoma is explained by the relative absence of cancer-related symptoms.[15] We realized that concentrating on differences at the level of diagnosis bears the risk of generalization: e.g., not all patients with testis carcinoma experience few problems upon their return to work. Cancer-symptoms are in general independent of the cancer site and treatment. We assumed that it is not simply diagnosis and treatment that hinders return to work, but rather the symptoms patients experience as a result of their diagnosis and treatment. In the study, we paid special attention to cancer-related fatigue. Cancer-related fatigue has been described as “the commonest and most debilitating symptom in patients with cancer.”[28] Fatigue is one of the best known and best-researched symptoms. Other equally relevant cancer-related symptoms are depression, sleep problems, physical

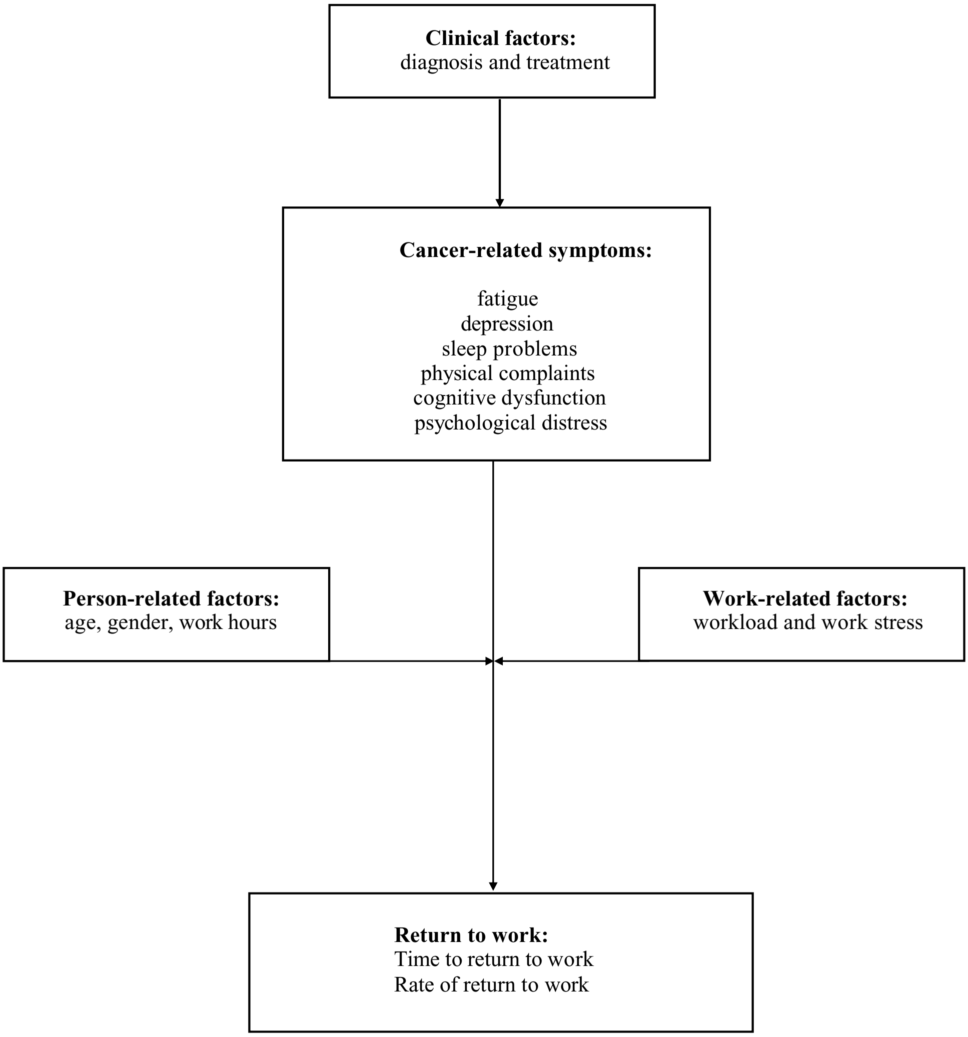

Figure 1. Model of the Impact of Cancer-Related Symptoms on the Return to Work of Cancer Patients, Controlling for Clinical Factors, Person-Related Factors and Work-Related Factors.

complaints, cognitive dysfunction, and psychological distress.[29–31] Cancer-related fatigue can have psychological and physical causes and is as such associated with the other symptoms, e.g., sleep problems or depression.

Cancer-related symptoms are not only highly prevalent in cancer patients, irrespective of the cancer site, but they are also likely to have an impact in a wide variety of work settings and may thus hinder the resumption of work. In addition to cancer-related symptoms, the impact of clinical, work-related, and subject-related variables[15] on the resumption of work needs to be considered, including diagnosis and treatment, physical workload,[1] work stress, age, gender, and work hours.[15] The aim of the study was to examine the relationship between fatigue and other cancer-related symptoms and the return to work in cancer patients, taking into account the impact of clinical-, work-, and subject-related factors. The impact of the symptoms was considered in a cohort of cancer survivors starting from 6 months following their first day of sick leave. The research question was: do the symptom scores at 6 months after the first day of sick leave predict the time taken to return to work and the rate of return to work at 12 months of follow-up? For a description of patients and methods, we refer to the original paper, here we want to concentrate on the results and their implications.

In our study, 64% of the cancer patients had returned to work at 18 months following their first day of sick leave. Fatigue levels at 6 months after the start of sick leave predicted the return to work at 18 months following the first day of sick leave. This was independent of the diagnosis and treatment, but not of other cancer-related symptoms. Age and physical workload were also independently related to the return to work. The other potential predictive factors like sleep problems, cognitive functioning, psychological distress, and work pressure were not significantly related to the return to work.

To our knowledge, this was the first longitudinal study in which the impact of cancer-related symptoms on the resumption of the work has been investigated in a systematic way. We were able to follow the cohort for a sufficiently long and appropriate period in which an additional 40% returned to work. The loss of patients during the follow-up was small. We studied factors that were important in predicting the return to work, identified from previous research. Within the cohort, there was a wide variety of symptoms and cancer types which facilitates the generalization of our results to cancer survivors in general. For all of the predictive factors, we used validated questionnaires.

The findings were in line with previous research that established the importance of fatigue and physical workload, in addition to diagnosis and treatment, but our study also showed that cancer-related symptoms are highly correlated.

Return to work is dependent on the nature of the social security system and many other social and cultural factors. This certainly influences the absolute rates of and time to return to work. In this study, the measures of association between the predictive factors and outcome measure are relative, comparing risks between subgroups of the cohort. This allows for a generalization across countries.

The interrelated nature of the cancer-related symptoms makes it difficult to disentangle potential relationships with the outcome measure. Even though the correlation coefficients were all far below 0.90, beyond which there would be too much collinearity, the statistical model yielded different results when all cancer-related symptoms were entered at the same time.[32] We chose a stepwise regression analysis in the final model to decide which predictors were most strongly related to the time taken to return to work. Due to multicollinearity, this result is arbitrary for cancer-related symptoms. Since fatigue is a component of many cancer-related symptoms, we feel that to improve the return to work rates fatigue should still be an important focus of attention.

Our study was based on a theoretical model that hypothesized that apart from fatigue, more cancer-related symptoms would influence the return to work. This turned out not to be the case for sleep problems, emotional distress, and cognitive dysfunction. For cognitive dysfunction, studies are needed that focus on different types of chemotherapy, resulting in specific cognitive dysfunction that may have remained obscured in our heterogeneous sample. Of the subject-related factors, this study only confirmed the previously found impact of age on the time taken to return to work.

To better predict problems encountered in the resumption of work, we need more knowledge about the process of returning to work in general. Qualitative studies could yield more insight into the processes that take place. These processes may be cognitive, e.g., "work will harm my health," may depend on social relations, e.g., "my spouse thinks it is too early to go back to work," or be dependent on the advice of the treating clinicians, e.g., "rest is the best cure for fatigue."

In our review of the return to work of cancer patients, we found that the percentage of cancer survivors varied from 30 to 93%, with a mean rate of 62% across all of the studies.[15] The findings of our study compare favorably with these results. However, patients who were very ill, in particular, and those who died were lost to follow-up. We cannot exclude that with the inclusion of some of these patients the rate of return to work would have been lower and the predictive value of the clinical factors could have been higher. This positive finding may also have been influenced by patients going back to work too soon. However, job satisfaction scores were relatively stable over time, with a score of 92.4 (S.D. 13.0) in the assessment taken prior to diagnosis, and a slightly, but not significantly, lower mean score of 89.7 (S.D. 17.5) for all of the survivors who had returned to work at 18 months following the first day of sick leave (range 0–100, where a higher score indicates more job satisfaction).

This study showed that cancer-related symptoms have an impact on social functioning with the important consequence of limiting the resumption of work, independent of other clinical and personal predictors. Curt advocated clear and well-established guidelines for the management of fatigue by physicians. The findings from our study underscore the need for such guidelines.[28]

6.0. DEVELOPMENTS SINCE THE REVIEW

Since the review, a number of papers and reports have been published that seem to underline the results from our prospective study.[2,3,9,33–35] In all, these papers underline the idea that now cancer patients do a lot better and that the next step should be taken. Job discrimination is no longer the issue. One editorial even speaks of "myth busting" referring to breast cancer patients having problems upon their return to work and referring to the excellent work of Elisabeth Maunsell and colleagues.[11] In a recent meta-analysis of employment of childhood cancer survivors, we found similar results. Employment in general was lower among survivors but varied with the type of cancer. For most types of cancer we could not show a difference in employment except for cancer that involved the central nervous system. For this group the risk of unemployment was almost five times higher among cancer survivors than among their healthy controls. A surprise finding from the meta-analysis was that survivors in North American studies did less well than those in European studies. It could be an indication that job discrimination in the USA has still more impact than in Europe.[36]

A recent IOM report speaks of a survivor care plan to better involve health workers in the care and attention for cancer survivors. In such a plan attention should be paid to interventions to improve return to work.[37]

7.0. INTERVENTIONS TO IMPROVE RETURN TO WORK

From the studies about risk factors we can conclude that experiencing a life-threatening disease like cancer has a big impact on working life for a couple of years at least. However, the variation in how patients deal with this life event is great. Some do not report sick at all and some never return to work. Depending on the diagnosis, the average number of months of being on sick leave is around 5 months.[3] This indicates a need for support in the return to work process. However, we do not know of any research in which this need has been studied and if patients experience a need for such support. It is our impression that when patients are offered support for return to work by their treating physicians this is highly appreciated. There is an urgent need for studies that evaluate interventions. In advance of such studies we will indicate what could be suitable interventions and outcomes to be studied. We will end with tangible advice that can be given to cancer survivors to improve the return to work process.

8.0. WHAT SHOULD THE PHYSICIAN DO?

In general, there are few theories that can guide physicians in how they can best support cancer survivors to return to work. Sickness absence and return to work after sickness can be viewed from many different points of view. There are many studies about factors that in general influence sickness absence in workplaces.[38,39] The economic impact of sickness absence and disability at the societal and company level is high. That is probably the reason that many studies address the economic or financial aspects of sickness absence. However, as mentioned before, especially return to work can be seen as a problem at the individual level as well. For most patients, work is an important aspect of their life and loss of work usually entails a substantial decrease in income. Thus, return to work can be seen as part of rehabilitation activities. In comparison to sickness absence in general or in comparison to the sickness absence related to back pain, the sickness absence of cancer survivors is a relatively small proportion and economically less important because the numbers are much smaller.

From a theoretical point of view, the WHO model of functioning indicates where possibilities for interventions can be found. The WHO explains in its International Classification of Functioning, Disability and Health how persons cope with their disability (Figure 2). The model states that working is one of the roles in which one can participate in society. Participation is strongly related to the ability to perform activities, which in turn is determined by the proper functioning of the body. Diseases or disorders affect this triad, possibly leading to disability depending on the conditions. Important conditional factors are of environmental and of personal origin.[16] The model offers three opportunities for intervention.

The first is better treatment. With successful treatment, the disease and its consequences will disappear. For example, a change in the treatment of heart disease greatly influenced its related disability in the 1970s and 1980s.[40]

Secondly, the environmental factors provide an opportunity for intervention. Adapting the environment can make the difference between retirement due to ill health or living an ordinary working life. The science of ergonomics has evolved around the concept of adapting the environment to workers.[41] This has always been a strong incentive for occupational physicians to advocate workplace adaptations to prevent disability. Usually these interventions are beyond the scope of clinicians.

Thirdly, the person-related factors, such as attitudes and opinions, form a natural focus for intervention for the clinician.

Studies that have investigated the prognosis of return to work among patients suffering from a variety of diseases confirm the idea gained from the WHO ICF model.[42–45] From our research we know that among cancer survivors the severity of the disease in terms of impact on physical integrity has the biggest influence on the

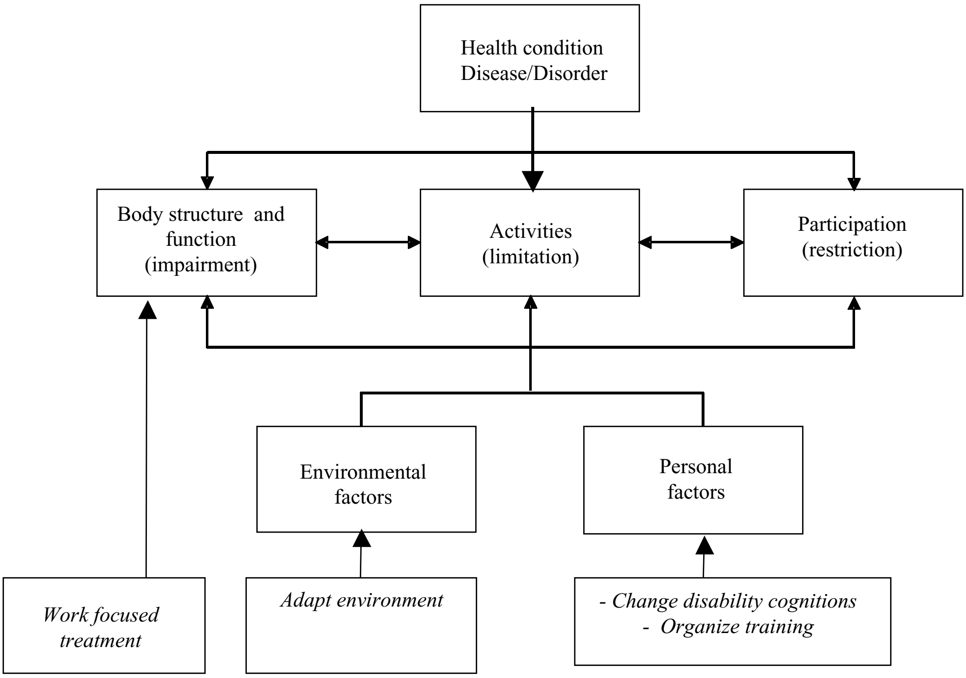

Figure 2. Points of Intervention Based on the WHO Model of Functioning.

time needed to return to work, but environmental factors and person-related factors play an additional role. There is still a lack of knowledge on person-related factors in return to work studies among cancer survivors. We know that for example the expectations patients with musculoskeletal disorders and mental health problems have about recovery predict the return to work best.[46] These are even better than the doctors' prediction.[47] This finding is in line with the model of Illness Representations. This theory states that the functioning of the patient is dependent on the idea that the patient has of the illness. The most important features of the illness representation are the cause (biologically versus functional), the time-line (long versus short), and the consequences for functioning. If the illness representations are not based on realistic medical knowledge, they can also be called misconceptions.[48] Based on this model, Petrie could show that long-term sickness absence was more frequent among patients with myocardial infarction that had misconceptions of their disease.[49] Subsequently, he could show in a randomized controlled trial that if these misconceptions of the illness could be changed by a cognitive behavioral intervention, the return to work rate was twice as fast.[50] We feel that this could also be a promising approach for cancer, where misconceptions about the disease and its consequences were very common until recently. However, we don't know of any research that has studied the prognostic value of cancer survivors' expectations or illness representations.

9.0. WHAT OUTCOMES SHOULD BE ADDRESSED?

Since the prognosis of return to work among cancer survivors is relatively good, it is not immediately clear what the outcome of interventions should be.

We would like to argue that, since there is still a gap in employment outcome for survivors compared to healthy controls, trying to narrow this gap should be the first target of interventions. Further, it is not clear how big the gap is in various countries. Employment status of back pain patients has been shown to be dependent on social security policies. In countries where it is easy to dismiss an employee because of health reasons, it will be more difficult to retain work.[51] For cancer survivors, apparently, more or different attention for the return to work is needed than currently given. In our research in the Netherlands, we found that in more than 50% of the cases treating physicians had not discussed work with their patients. On the other hand, the physicians that participated in our studies were surprised to find out how well their questions about working life were received by their patients.[52] In many countries, return to work policies create considerable confusion among physicians, which might explain why there is this apparent lack of attention for this problem.[53]

A second outcome to address should be a shorter time to return to work. There is some evidence that the longer employees are off work the more difficult it is to return. In other words, with long spells of sickness absence the chance of returning to work diminishes over time. Although there is a wide variation, for many cancer survivors the time to return to work is in the magnitude of several months' absence from work. Therefore, it would be beneficial if the time to return to work could be shortened or otherwise optimized.

A third outcome could be to decrease the number of cancer survivors that stop working for health reasons. In Maunsell's study, the 20% of cancer survivors that stopped working did so because they said they wanted to themselves. Half of them said that this was because of health reasons.[3] The precise meaning of this statement is unclear, but it fits well with the notion that perceived disability is the best predictor of return to work. It could be that the stopping because of health reasons was based on a misconception that it is more beneficial for health to stop working.

10.0. WHAT SHOULD BE THE TARGET OF OUR INTERVENTIONS?

We can think of three possible pathways to influence the return to work outcomes. First of all, less invasive treatment and less side effects of treatment will also improve return to work rates. Scandinavian research showed that breast conserving surgery and day surgery was related to significantly shorter sick leave than more invasive surgery and overnight care respectively.[54] Since the search for better treatment methods is good in itself we can leave this to the oncologists.

The second pathway would be through the better treatment of cancer-related symptoms. Fatigue and depression seem to be the most promising ones since they predicted return to work independent of diagnosis and treatment in our research. Also here, there has been substantial research effort directed at ameliorating the cancer-related symptoms.[55–57] However, none of these studies took into account that this could also lead to better functioning including return to work. We would advocate that those who study interventions to improve cancer-related symptoms use return to work as an outcome measure. For practitioners, we suggest that cancer survivors be referred to rehabilitation programs that address fatigue and depression.

The third pathway would be to look at other prognostic factors. If patient expectations are predictive for return to work also for cancer survivors, programs should be devised to address misconceptions. This seems a promising approach but it has to be substantiated by research before it can be applied in practice.

The fourth and most practical pathway would be to improve current return to work strategies and to apply existing knowledge from other areas to cancer survivors as advocated by Feuerstein.[58] From research in the back pain area we learned that patients perceive a lack of instructions how to cope with symptoms and limitations in daily practice. Since work is not very often discussed with cancer patients we assume that this is similar for cancer survivors. Therefore, we made a list of items based on rehabilitation principles with the most concrete instructions that we could find for return to work.

The first principle we used was that of goal-oriented rehabilitation.[59] Goal setting provides the opportunity to work toward a concrete goal and being able to evaluate the activities against the goal that was set. In terms of return to work this means that we advise cancer survivors to make a concrete plan for work resumption. The plan should contain the tasks to be taken up first and the dates when this is going to be done.

The second principle is that of graded activity. There is some evidence from back pain and chronic fatigue research and some underpinning with cognitive behavioral theory that gradually increasing the activities according to a preset fixed scheme is beneficial. The final goal of return to work is set consistent with the patient's wishes.[60,61] However, this fixed plan contrasts with the often expressed wish of cancer patients to work at the moments they feel well and to stop working when they have an off day. A worthwhile research question would be to determine whether the graded activity approach is more beneficial for return to work then a simple volitional approach. Patients sometimes are afraid to make plans because they feel so unsure that they feel it is impossible to predict what would be a reasonable goal to set. To overcome this problem we advocate the drawing up simultaneously of a second scheme or plan that can be used when the first plan proves to be too ambitious.

The third principle that we use is that of involving the supervisor right from the start to facilitate at least temporarily work accommodations. The use of participatory ergonomics which seems to be successful in return to work of back pain patients should assist cancer survivors as well.[62]

The principles were translated into a 10-step plan for return to work that we tested among cancer survivors at the radiotherapy department (Table 1). In general, the plan was appreciated except for the idea of having a simultaneous second scheme. This item seemed difficult to understand. Not all patients were keen on making a fixed scheme because they felt it was better to start working according to how they felt. Nevertheless, it seems a tool that meets the wish of more concrete instructions.

11.0. CONCLUSION

Much has changed over the course of 30 years. Improved diagnosis and treatment has increased survival and increased attention to societal reintegration. In the early years, attention focused almost exclusively on job discrimination, legal, and insurance issues. While these continue to challenge the cancer survivor the focus of attention has shifted. Attention to job discrimination and legal issues has resulted in less discrimination and some improvement in insurance coverage.[33] Research has expanded to other factors that hinder the return to work of cancer patients.[14,15] While the disease itself and its treatment still have the most impact on the return

Table 1. Ten Steps to Return to Work

1. Schedule an appointment with your occupational health physician as the professional who is there to help you with return to work.
2. Keep in contact with your employer. You will need him or her to get back to work and to realize work accommodations if needed.
3. Keep in contact with your coworkers. Go to work to see them and tell them how you are doing.
4. Draw up a return-to-work plan in consultation with your supervisor and occupational physician. For all involved, supervisor and colleagues, the plan will make your situation more transparent and at ease.
5. Start to return to work before full recovery, but start with a very limited number of hours. Starting with a small number of hours brings the reassurance that this will succeed.
6. Make sure the return-to-work plan encompasses the date and number of hours of the start, which days of the week will be worked, the timing of the expansion of hours, the tasks and number of hours of this expansion, and the proposed date of full return to work.
7. How to set a goal for the time needed for complete return to work? It is not possible to give a concrete advice, because it depends on the number and the severity of the complaints and the nature of the work how long it will take.
8. Evaluate the return-to-work plan with your supervisor every 2 weeks. Adjust the plan according to your evaluation.
9. If unsure, draw up a second, less ambitious return-to-work plan that may be used if the first plan fails.
10. An example of a return to work plan is given in which gradual return to work is scheduled for a nurse who has survived breast cancer in 12 weeks time starting with two times 4 hours per week.

to work of cancer patients successfully, managing cancer-related symptoms such as fatigue and depression can also influence work resumption. Physically demanding work makes it more difficult to resume work. There is a need to study other prognostic factors such as patients' expectations of functioning. They form a potential focus for intervention.

There is still a lack of interventions and evaluation of intervention studies. It can be expected that better treatment leads to an increase in return to work. Improved treatment of cancer-related symptoms should also improve time to return to work. However, progress from research has been impeded by weak research designs and haphazard measurement of work outcomes.[9]

In conclusion, cancer has a distinct impact on work outcomes. The issue of return to work of cancer patients is an important one which needs to be better addressed by treating physicians and other health care workers. Research should not only be directed at prognostic factors but also at developing and evaluating interventions that enhance return to work with more rigorous research designs.

Evidence-based guidelines for return to work of cancer survivors must await specific clinical trials, however at this point, can be best based on general rehabilitation principles. These include: establish concrete goals, increase workload gradually according to a fixed plan, and involve management for work accommodations.

These guidelines could form the basis of the earlier mentioned survivor care plan to better involve health care workers in the care and attention for cancer survivors. In addition, such a plan should incorporate interventions to improve return to work. Because, despite obvious improvements, cancer patients still face problems in the workplace and they have to cope with the aftermath of a diagnosis and treatment which has a significant impact upon their lives and well-being. A thorough survivor care plan should aid patients in making the transition back to work as uncomplicated as possible.

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Chapter 22

Comprehensive Long-Term Follow-up

Cancer Survivorship Centers

Linda A. Jacobs, Jane Alavi, Angela DeMichele,
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1.0. INTRODUCTION

Cancer survivors experience a number of physiological and psychological sequelae, called late effects, as a consequence of their cancer treatment. In pediatric oncology, late effects of treatment have been studied for over two decades,[1–2] and are therefore better understood than late effects as a result of cancer treatment during adulthood. However, identified late effects in adults include diverse phenomena such as decreased cognitive functioning in breast cancer survivors[3] and increased cardiovascular morbidity in testicular cancer survivors[4] compared to non-cancer controls. Although adults over 65 years of age comprise more than 60% of cancer survivors, little attention has yet been directed toward the long-term sequelae particular to older adult cancer survivors.

As the public health phenomenon of cancer survivorship grows, creative and diverse models must be developed to address the long-term needs of adult cancer survivors. Systematic approaches are needed within a variety of health care delivery settings in order to reach and respond to these growing millions, including both primary and specialty care settings. This chapter will provide some background information regarding the care and surveillance recommendations for pediatric and adult cancer survivors over the last few decades, and discuss the development, essential components, and ongoing evolution of the first adult cancer survivorship program in the country, the Lance Armstrong Foundation (LAF) Living Well After Cancer (LWAC) Program at the Abramson Cancer Center of the University of Pennsylvania. Other adult survivorship programs currently in existence and under development across the country will also be discussed.

2.0. HISTORICAL PERSPECTIVE

2.1. Initiatives in Pediatric Oncology

In the decades of the 1960s and 1970s, it became clear that the aggressive treatment of pediatric cancers had come at a cost to the survivors. Along with continuing improvement in cure rates, there were new problems appearing, including growth retardation, cardiac and pulmonary disease, neurological and cognitive disorders, and second malignancies. Studies of small groups of survivors in individual centers produced important data on these late effects as they became known, but statistical significance could not be achieved without larger multi-institutional research. Therefore, the Late Effects Study Group was formed in the 1970s. This consortium of 13 pediatric centers in North America and Europe performed a retrospective review in 1978.[5] This group recorded the sequelae in 369 survivors of childhood cancer, all of whom had been diagnosed in 1972, thus permitting a 5-year follow-up. The results suggested that the medical problems experienced by survivors were likely to increase over time and that prospective, rather than retrospective studies would be required.

Thus, the first program for the systematic follow-up of pediatric cancer survivors was organized in 1983 at The Childrens' Hospital of Philadelphia (CHOP), by Anna Meadows and Wendy Hobbie.[6] Eligible patients were those whose diagnosis had been made in 1970 or later and were diagnosed with cancer at any age up to 16 years. These survivors had not received treatment for their cancer in the last 2 years, and were alive at least 5 years since the date of diagnosis or since the last evidence of the disease. The patients were given a standardized physical examination, growth plots were maintained, and laboratory or radiological studies were ordered on an individual basis, depending upon the diagnosis, specific treatments, complications, and preexisting conditions. The focus of the clinic was to provide continuity of care with systematic evaluation and treatment as necessary. Research was also an important goal. In the first report of the results of this program, the investigators described that late effects of treatment or disease were present in 73% of the patients, and 41% were severely affected.[6]

Soon after the establishment of the clinic in Philadelphia, other pediatric centers organized follow-up programs. The After Completion of Therapy Clinic (ACT) was established at the St. Jude Children's Research hospital in 1984, and in 1987, a Long Term Survivors Program was started at Golisano Children's Hospital in Buffalo. By 1993, there were approximately 30 such programs in the United States.[7] In a survey in 1997, Oeffinger found that 53% of centers which treated childhood cancer had long-term follow-up programs. Ninety-three percent of these programs were directed by a pediatric oncologist and 70% were also staffed by a nurse clinician or nurse practitioner.[8]

Currently, most of the programs have similar criteria for patient recruitment and offer similar follow-up studies. Patients are usually accepted if they completed cancer treatment at least 2 years earlier, and have been free of the disease for 2–5 years. In general, patients are under 18 years of age at entry into the program, and are often referred elsewhere for further follow-up at the age of 18. The patients are generally evaluated yearly, or more frequently in specific situations, such as during puberty. The goals for such programs are stated in the website of the Golisano Children's Hospital (www.stronghealth.com/services/childrens/patientcare/hemonc/survivorcare.cfm): "to provide monitoring and counseling regarding late effects of therapy. These programs are not designed to be a primary clinic for these survivors but rather to complement care delivered by primary care providers. In addition to providing patient care and follow-up, these clinics are an educational and advocacy resource for patients, families and other health providers."

Follow-up programs are expanding their roles since the first programs were established, and today they often include social workers, counselors, and a group of specialists available for referrals. Institutions that are members of the National Cancer Institute-funded pediatric cooperative group, the Children's Oncology Group (COG), are required to have on-site follow-up programs. Consequently, the follow-up of childhood cancer survivors is in some ways made easier by the extent to which children with cancer are treated in specialized centers that are for the most part members of the COG. It is estimated that 50–60% of children with cancer are initially treated in these specialized cancer centers; however, only 40–45% of these patients receive follow-up care in specialized centers and relatively few of these centers have comprehensive, multidisciplinary programs.[9] Despite these statistics, there are even fewer programs available for adult cancer survivors.

In addition, the COG, in collaboration with the nursing discipline and the Late Effects Committee, developed *Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Survivors* that were released in March 2004 and can be found on the web at www.survivorshipguidelines.org. These guidelines represent a statement of consensus from a panel of experts in the late effects of pediatric cancer treatment. The recommendations are based on a thorough review of the literature as well as the collective clinical experience of the task force members, panel of experts, and multidisciplinary review panel (including nurses, physicians, behavioral specialists, and patient/parent advocates). Implementation of these guidelines is intended to increase awareness of potential late effects and to standardize and enhance follow-up care provided to survivors of pediatric malignancies throughout the lifespan.

The *Long-Term Follow-Up Guidelines* were developed as a resource for clinicians who provide ongoing health care to survivors of pediatric malignancies. A basic knowledge of ongoing issues related to the long-term follow-up needs of this patient population is assumed. The screening recommendations in these guidelines are appropriate for asymptomatic survivors of childhood, adolescent, or young adult cancer presenting for routine exposure-based medical follow-up. More extensive evaluations are presumed, as clinically indicated, for survivors presenting with signs and symptoms suggesting illness or organ dysfunction. As new information becomes available, the guidelines will be updated periodically to reflect those changes. The COG recommends that clinicians check the COG website periodically for the latest updates and revisions.

3.0. FOLLOW-UP CARE FOR ADULT CANCER SURVIVORS

There have been a few studies examining screening behaviors of cancer survivors or exploring the non–cancer-related health care that survivors receive. Adult cancer survivors represent a steadily growing vulnerable population of patients who may not be receiving optimal care for non–cancer-related issues.[10] Although there are studies reporting that cancer survivors have higher cancer screening rates than individuals without a cancer diagnosis,[11] an extensive review of relevant studies from 1966–2005 suggested that the cancer survivor is at risk for many problems most likely related to the treatment received for their cancers.[12] No recommendations exist for screening among adult cancer survivors. As long-term health issues specific to cancer survival are emerging as a public health concern, the medical community as well as adult cancer survivors and their families are contemplating and exploring the best venue for providing appropriate comprehensive follow-up care.

The adult oncology community has lagged significantly behind pediatric oncology in the development of survivorship follow-up programs, surveillance guidelines, as well as research with this population. In 2006 the Institute of Medicine (IOM) of the National Academies published a report by a committee that was established to examine the range of medical and psychosocial issues faced by adult cancer survivors, and to make recommendations to improve their health care and quality of life.[13]

These guidelines provide direction for those caring for adult cancer survivors until more specific data-based adult surveillance guidelines are developed. The IOM undertook the task of putting together a committee to examine the range of potential medical and psychosocial issues experienced by adult cancer survivors and produce a report focusing on the phase of care that follows primary treatment. The IOM report, *From Cancer Patient to Cancer Survivor, Lost in Transition,* was released on November 7, 2005 and the aims of this report are to:

1. Raise awareness of the medical, functional, and psychosocial consequences of cancer and its treatment.
2. Define quality health care for cancer survivors and identify strategies to achieve it.
3. Improve the quality of life of cancer survivors through policies to ensure their access to psychosocial services, fair employment practices, and health insurance.

The committee's findings and recommendations are directed toward cancer patients and their advocates, health care providers and their leadership, health insurers and plans, employers, research sponsors, and the public and their elected representatives. This report can be found on the web at www.iom.edu. The IOM report is an excellent first step toward raising awareness, and the debate continues regarding who should be providing care to the adult cancer survivor and where should this be happening. It is becoming apparent that there is no single answer to this issue. The many factors that must be considered include insurance, region of the country, and institutional-, disease-, and patient-specific factors.

As mentioned earlier, surveillance guidelines for the management of adult cancer survivors do not exist; however, the American Society of Clinical Oncology (ASCO) has taken the lead to begin the development of guidelines thus laying the foundation for the ongoing development of disease and treatment specific guidelines as data become available regarding late effects of treatment.

3.1. Surveillance Guidelines

In order to determine the oncology community's understanding of follow-up care for the adult cancer survivor, ASCO performed a survey of over 800 members who are mostly medical oncologists.[14] A substantial proportion of the members surveyed stated that they would like more education and training with respect to caring for long-term cancer survivors. In addition, the survey demonstrated that 73% of oncologists believe that they should provide continuing care to cancer survivors; 32% of oncologists report that they "always" provide ongoing general medical care, including health maintenance, screening, and preventive services to cancer survivors in their practices; 47% of oncologists report that they "sometimes" provide these services; and 2% of oncologists report that they feel comfortable providing these services. Presently, no clinical practice guidelines exist to direct the health professionals in providing this care.[14]

In January 2005, ASCO formed the "Expert Panel on the Long-Term Medical Care of Adult Cancer Survivors," charged with the development of evidence-based clinical practice guidelines. The Panel is cochaired by Charles L. Shapiro, MD of Arthur James Cancer Hospital of Ohio State University and David J. Vaughn, MD of the Abramson Cancer Center of the University of Pennsylvania. The purpose of the proposed guidelines is "to provide health professionals with the knowledge and expertise to decrease morbidity and to improve the quality of life for adult survivors of cancer."[5] The Panel is comprised of experts from the fields of medical oncology, radiation oncology, surgical oncology, behavioral science, cardiology, primary care, and patient advocacy.

The Panel created four working subgroups to identify important questions, review the literature, and develop clinical practice guidelines. The four working groups reflect the Panel's identification of four major topics to address in the proposed guidelines: (1) Cardiovascular morbidity and late cardiovascular effects of treatment in long-term adult cancer survivors; (2) Hormone replacement, osteoporosis, and sexual dysfunction in long-term adult cancer survivors; (3) Second cancers and cancer screening in long-term adult cancer survivors; and (4) Psychosocial concerns in long-term adult cancer survivors. The timeline set for the Panel will result in a final product for dissemination to members in the next few years.

3.2. The University of Pennsylvania Model of Care

In 2001 the LAF provided funding to support the development of an adult cancer survivorship program at the Abramson Cancer Center of the University of Pennsylvania. As a dedicated cancer survivorship program embedded within an NCI-designated Cancer Center, the LAF LWAC Program is the first adult cancer survivorship program in a specialty care setting. Dr. Anna Meadows of The Children's Hospital of Philadelphia, acquired the funding through a grant proposal to the LAF, and Linda Jacobs, PhD, RN was recruited to direct the development and all aspects of the program. The multidisciplinary composition of the LAF LWAC Program team has expanded over time and the director's leadership remains the central organizing element. Members of the team include the director of the program, an oncology advanced practice nurse who is a doctoral student studying the late effects of cancer treatment on older breast cancer patients, a behavioral scientist, a medical oncologist who specializes in urologic cancers, a breast oncologist, Dr. Anna Meadows and another general oncologist with an interest in survivors of childhood cancers, a cardiologist who focuses on the cardiovascular late effects of treatment, a cancer rehabilitation specialist, an exercise physiologist, a primary care provider with an interest in complementary and alternative medicine use for the late effects of cancer treatment, two psychosocial counselors, and a nutritionist.

The Penn survivorship program is a research, clinical, and education focused multidisciplinary effort that has evolved and expanded over the last 5 years. The LAF LWAC Program team meets on the third Monday of every other month to discuss program development, clinical issues, ongoing research projects, and ideas for new projects. Team members also report on presentations, special projects, and publications. The program components will be described in the following sections.

3.3. Research Program Component

Between 2001 and 2002 the LAF LWAC Program team focused on program development and it was determined that the establishment of a research focus was critical to the success of the program for a number of reasons: (1) surveillance guidelines had not been established for adult cancer survivors; therefore, survivorship research protocols needed to be developed that focus on the clinical issues identified by survivors and their providers; and (2) research funding is necessary to support the program.

A research database was established, questionnaires developed, and tools were chosen to evaluate the medical and psychosocial aspects of the survivorship experience. In addition, research proposals have been funded and the team continuously works to develop, refine, and submit new proposals based on clinical evidence gathered in the clinical component of the program. We have generated some preliminary data on characteristics of cancer survivors who have participated in the program to date that should provide a general overview of some of the highlights of patient sample that we have seen thus far. In the first 2 years of the program, we saw breast and testicular cancer survivors who were approximately 24 months since diagnosis. Figure 1 presents the pattern of symptoms reported by the breast cancer survivors. We also observed a significant relationship between number of symptoms reported and quality of life (Figure 2). The types of supportive services used by the breast cancer survivors are illustrated in Figure 3 and types of preventive health screenings this group sought are indicated in Figure 4. Related to maintenance of health over the long run we did observe that among the testicular cancer survivors attending the clinic (Table 1), a number of risk factors related to cardiovascular disease was observed, highlighting the importance of long-term monitoring for overall preventive health in cancer survivors and not just a focus on cancer surveillance (Figure 5).

3.4. Clinical Programs

The development of the clinical component of the LAF LWAC Program has been a challenge. Initially the plan was to develop a clinical care center for cancer survivors who were 2 years since diagnosis and collect vital information on each survivor that would be entered into a database. However, after a year of piloting the clinical programs with testicular and breast cancer survivors, it was evident that more than one model of care was needed to meet the needs of patients as well as the Cancer Center.

It was determined that what has been identified as *practice and consultative models* would be developed and further piloted at Penn again with the breast and testicular cancer survivors. Testicular cancer survivors were an excellent choice of patients for the *practice model* since this is a relatively small group of patients who are seen by one oncologist at Penn. In addition, testicular cancer is a good model of a curable neoplasm. These patients are generally young when diagnosed, and following these patients prospectively allows the survivorship program staff to explore the possibility of subclinical late effects and incorporate screening for late effects into follow-up visits.

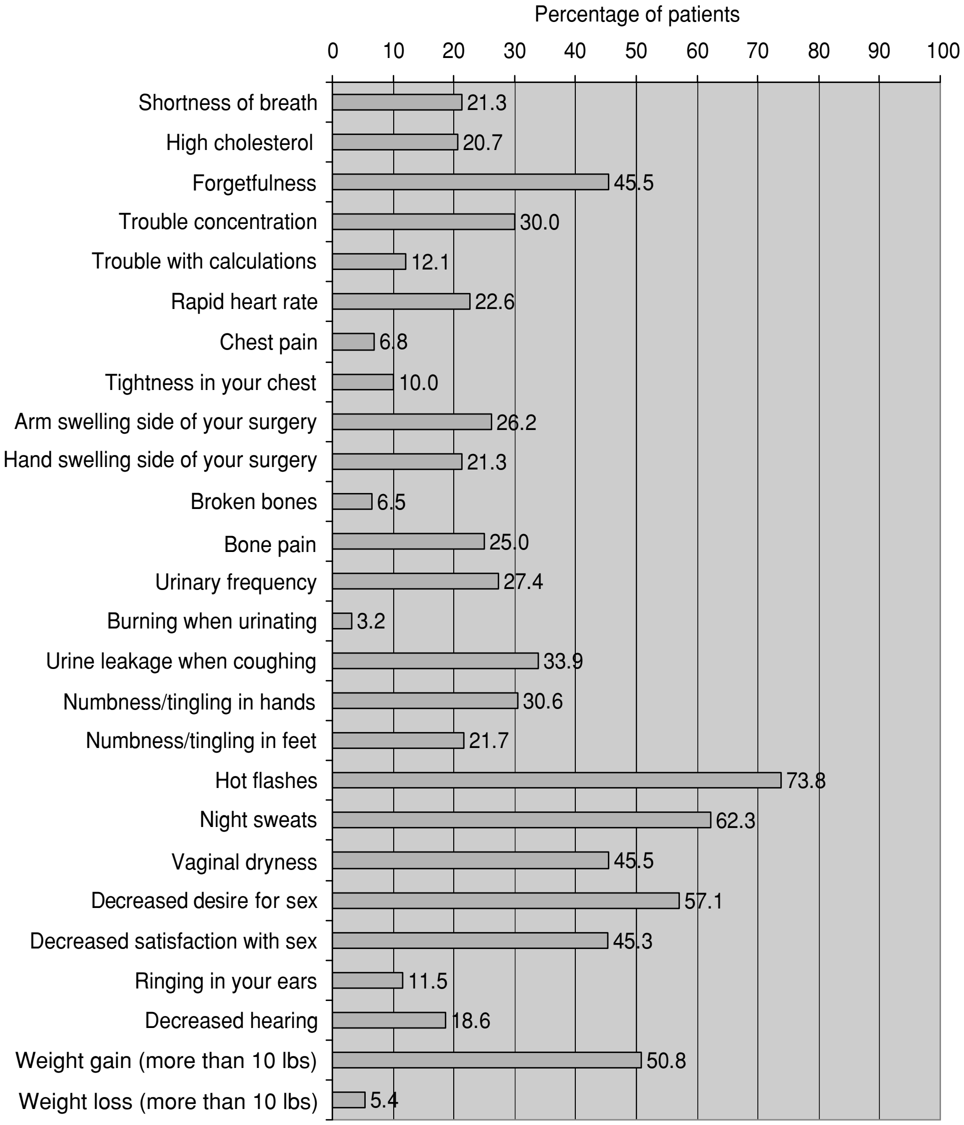

Figure 1. Patterns of Symptoms Among Breast Cancer Survivors ($N = 63$).

The *practice model* is designed with the intention of providing routine follow-up care, and monitoring for recurrence while at the same time developing an individual risk profile for late effects of treatment based on age, family history, comorbidities, and cancer treatment history. The practice model has been expanded over the last few years to include survivors of Hodgkins and non-Hodgkin lymphoma, and more recently to include young adult survivors of childhood cancers. A transition program between the oncology programs at CHOP and the Abramson Cancer Center at Penn has been established and patients over the age of 21, followed in the Late Effects Clinic at CHOP, are referred to the LAF LWAC Program for follow-up. This program has been very successful and efforts are in place to assure that clinical and research programs with this group of survivors will flourish in the years ahead.

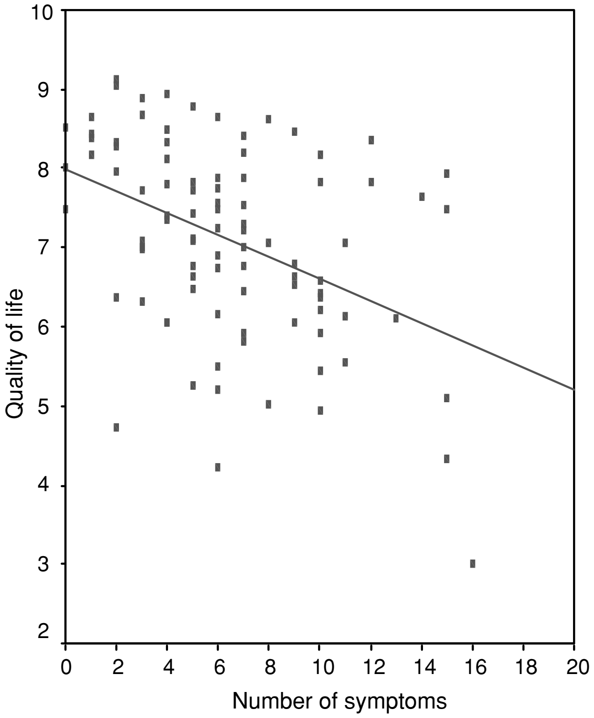

Figure 2. Relationship Between Number of Symptoms and Quality of Life Among Breast Cancer Survivors 2–5 Years Postdiagnosis ($N = 93$).

The breast cancer survivors' clinical program was very difficult to pilot and it became evident quickly that a different approach would be needed to manage breast cancer survivors. The breast cancer program at Penn is a large clinical and research focused effort with several medical oncologist/oncology nurse practitioner collaborative practice teams caring for patients. In addition to the large volume of patients that mandates a separate clinical program with dedicated staff for breast cancer

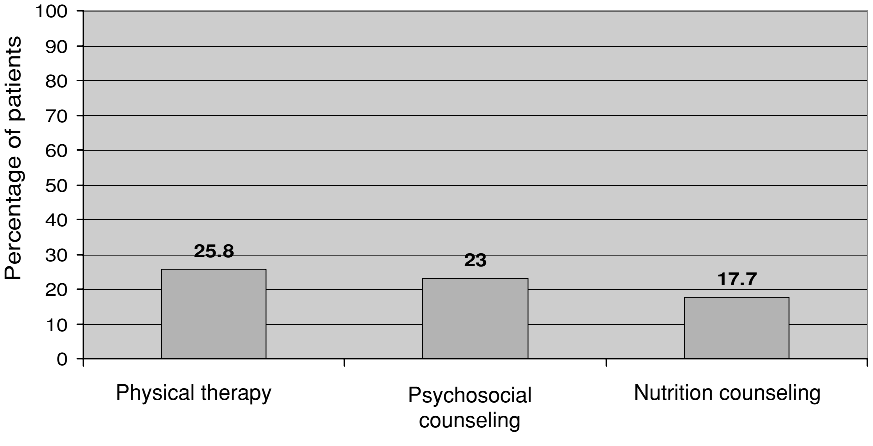

Figure 3. Use of Supportive Services by Breast Cancer Survivors ($N = 63$).

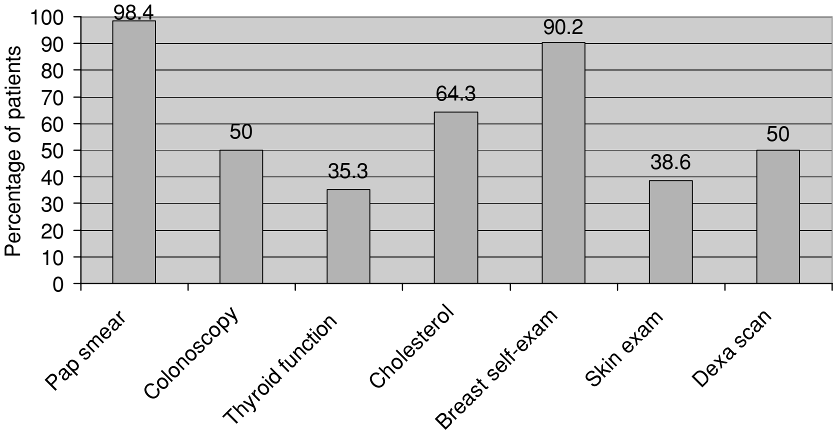

Figure 4. Breast Cancer Survivors Preventive Health Screening ($N = 63$).

survivors alone, the issue of continuity of care with the primary oncology practice teams was an important consideration. Consequently, the LAF LWAC Program team determined that a *consultative model* approach would be piloted next with the breast cancer survivors. This model is structured as a research protocol outlining specific aims, as well as a series of questionnaires and tools that are used to collect primarily symptom and quality of life data. An already existing breast cancer database in the Rowan Breast Center at Penn was used to identify potential subjects. These patients are then followed prospectively with yearly mailings of study packets. Although patients were initially identified at 2 years postdiagnosis, it was determined that it would be most useful to collect baseline data when the patients present at diagnosis. In that

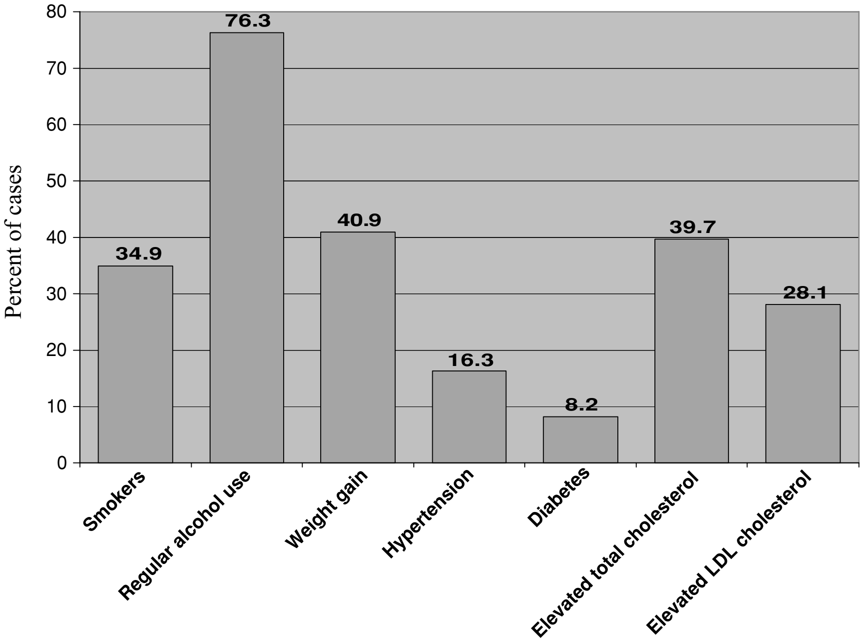

Figure 5. Cardiovascular Risk Factors Among Testicular Cancer Survivors ($N = 53$).

Table 1. Early Breast Cancer Survivor Cohort Attending Clinic ($N = 63$)

Median age, years (Range)	51 (26–77)	
	Frequency	Percent
Marital Status		
Single	8	12.7
Married	40	63.5
Divorced	9	14.3
Lives With Partner	2	3.2
Separated	1	1.6
Widowed	3	4.8
Breast Cancer Staging		
Stage I	24	38.1
Stage II	38	60.3
Stage III	1	1.6
Race/Ethnicity		
White/Caucasian	50	79.4
ER Status		
Negative	6	9.5
Positive	56	88.9
Not Reported	1	1.6

way data is collected through and posttreatment, providing a broader, clearer picture of the survivor's experience. The questionnaires used to collect data with the breast cancer survivors were designed and tested over the first year of the program in the clinical model and have been refined as the program evolved. Similar questionnaires are used with the other survivors seen in the clinical programs and will be used more broadly as the consultative program is expanded to include other cancer sites. Questionnaires are designed and revised to focus on population specific issues. The model was initially designated as *consultative* since the initial goal of the program was to gather clinical data on self-report questionnaires, enter this data into a database, and provide the primary oncology team with a list of issues reported by survivors.

The consultative pilot project has recently ended and the protocol is being revised to reflect necessary changes including contacting the patients with recommendations rather than providers, that were identified during the pilot. The LAF LWAC Program team is currently developing a few additional innovative ways to address clinical issues reported by survivors on their questionnaires, such as summarizing these symptoms in a letter to the patient rather than their providers so that patients can discuss the management of these issues with the appropriate provider, e.g., their internist, oncologist, gynecologist, cardiologist, etc. The survivorship program team is also planning to expand their efforts to include more survivorship-focused talks at each of the Penn annual disease-specific conferences. In addition, informal consultation is available to the clinical practices regarding surveillance recommendations for late effects of treatment that may be related to surgery, chemotherapy, or radiation, as well as management strategies for symptoms resulting from the late effects of treatment. The nurse practitioners in the collaborative oncology practices at Penn have a major role in managing the care of and symptoms reported by cancer survivors.

The consultative program has been successful in identifying and managing problems associated with survivorship. The effort provides an opportunity for the LAF LWAC Program team to heighten the awareness of late effects of treatment among the primary oncology practices and specialty care providers. The long-range plan is to extend this model to other disease-specific oncology practices at Penn with one of the nurse practitioners/MDs teams caring for a specific population taking the lead for managing the protocol with and identifying that group of eligible patients.

4.0. DEVELOPING ADULT CANCER SURVIVORSHIP PROGRAMS ACROSS THE COUNTRY

The IOM report identified a few academic centers that developed adult cancer survivorship follow-up clinics over the last few years and described many of the problems related to the development, the daily operation, and support for these new initiatives. The report identifies that there are relatively few adult cancer survivors who are cared for in specialized survivorship clinics despite the fact that specialty care clinics for pediatric cancer survivors is a very acceptable model for the care of this population. In fact, there are 35 comprehensive pediatric follow-up programs across the country. These programs vary and while some focus exclusively on a specific population of cancer survivors, e.g., pediatric survivors of a bone marrow transplant (Milwaukee Regional Medical Center), most of the pediatric cancer survivorship programs focus on survivors of any type of cancer. A listing of pediatric and young adult programs that were identified through a survey done across the country is provided in Table 2. There is really no way of knowing if this list is all-inclusive since there are no reliable resources that identify and describe all of the cancer survivorship programs across the country. To date there are no published listings outlining adult survivorship programs in the United States or internationally. The adult programs outlined in the IOM report, include: the University of Texas, M.D. Anderson Cancer Center Life After Cancer Care that is focused mainly on breast cancer survivors, the University of Michigan Breast Cancer Survivor Clinic, Dana Farber Institute: LAF Adult Survivorship Clinic that is in the development phase, and the LAF LWAC Program at the Abramson Cancer Center of the University of Pennsylvania. In addition to these programs, the Princess Margaret Hospital Breast Cancer Survivorship Program Canada is described on the web when survivorship programs are searched. These programs are not well described and it is unclear how these programs function or to what extent services are provided to adult cancer survivors. It is evident from the paucity of information on adult cancer survivorship programs and from the limited number of programs identified that the oncology community must focus more effort on exploring how the needs of adult cancer survivors can be adequately met. The survivorship program at Penn continues to evolve as more research is conducted that examines the long-term physiologic and psychosocial consequences of a cancer diagnosis and treatment. This program will continue to be a model for the development of survivorship programs across the country in the years ahead.

5.0. FUTURE DIRECTION

The numbers of adult cancer survivors is growing, and the number of young adults who have survived childhood cancers has and continues to increase. Models of care must anticipate the needs of these populations. As institutions across the country develop survivorship centers, they will need to determine the model that works best

Table 2. Pediatric and Young Adult Cancer Survivorship Programs

California
Childrens Hospital Los Angeles
LIFE Program (Long-Term Information, Follow-up and Evaluation)
4650 Sunset Blvd. #54
Los Angeles CA 90027
Coordinator contacts: Mary Baron Nelson, MS, RN, CPNP, CPON
Medical Director: Clarke Anderson
For further information about the program/appointments contact: (323) 669–2489
Web site: LIFE program at Childrens Hospital, Los Angeles
Sees both child and adult survivors; provides referrals for adults.
City of Hope National Medical Center
Long-Term Follow-up Clinic for Survivors of Childhood Cancer
1500 E. Duarte Rd.
Duarte, CA 91010
Wendy Landier, RN, MSN, CPNP—coordinator
Smita Bhatia, MD
(626) 301-8426
(This clinic is generally scheduled once a month, but during summer and other off-school times, the clinic meets more as per demand, scheduling as many clinics as necessary.)
Colorado
Denver Children's Hospital
HOPE Clinic
1056 East 19th Ave, B115
Denver, CO 80218
Amanda Louey, RN BSN—coordinator
303-864-5441
Brian Geffe, MD
303-861-6776
Florida
Nemours Children's Clinic
Hem/Oncology Clinic
807 Children's Way
Jacksonville, FL 32207
(800) 767-5437, extension 3761
Annie Rini, RN, BSN—coordinator
Rotating doctors
Follows children up to age 21, then transitions to adult primary care providers.
Georgia
Children's Healthcare of Atlanta
Cancer Survivor Program
1405 Clifton Road
Atlanta, GA 30322
Melissa Hamilton, RN MS CPNP: (404) 315-2717
Lillian Meacham, MD 404-727-8232
Illinois
Children's Memorial Hospital
Long-Term Follow-up Program
2300 Children's Plaza
Chicago, IL 60614
Barbara Lockert RN 4151: 773 880-4151
Reggie Duerst, MD
Treats child and teens
Children's Memorial Hospital
Northwestern Medical Faculty Foundation
Star Program for Young Adult Survivors
Survivors Taking Action & Responsibility Comprehensive Care for Survivors of Pediatric Malignancies
675 N. St Clair 18-200
Chicago, IL 60611

Table 2. (*Continued*)

Arlina Ahluwalia, MD, Director
Karen Kinahan, MS, RN Clinical Nurse Specialist (312) 695-4979
Treats survivors over 21 years old.

Indiana

Riley Hospital for Children
Indiana University School of Medicine
Childhood Cancer Survivor Program
Riley 4340
702 Barnhill Drive
Indianapolis, IN 46217
Coordinator: Ann Haddix, RN, CPNP, 317-278-0199
Medical Director: Terry Vik, MD, 317-274-8784
We see both Children and Adults
Clinic Appointments 317-274-2143 or 800-238-8399

Maryland

Johns Hopkins Oncology Center
Long-Term Follow-up Clinic
600 N. Wolfe St Park 2 clinic
Baltimore MD 21287
(410) 614-5062
Kathy Ruble RN—coordinator
Cindy Schwartz MD
Web site: none, but on the Hopkin's site is a good article about Cindy Schwartz.

Massachusetts

Dana-Farber Cancer Institute
David B. Perini, Jr. Quality of Life Clinic for Childhood Cancer Survivors at 44 Binney St.
Boston, MA 02115
617-632-5124
Ellen E. Casey—Coordinator
Lisa Diller, MD
Web site: David B. Perini Quality of Life Clinic Sees children and adults.

Dana-Farber Cancer Institute
Pediatric Neuro-Oncology Outcomes Clinic
44 Binney St, SW 331
Boston, MA 02115
617-632-2680
Christine Chordas, PNP
Christopher Turner, MD
Web site: Pediatric Neuro-Oncology Outcomes Clinic
Sees children and adult survivors of pediatric brain and spinal cord tumors.

Michigan

University of Michigan
Long-Term Follow-up Clinic
Department of Pediatric Hematology/Oncology
1500 East Medical Center Dr.
Ann Arbor MI 48109
(734) 936-9814
Marcia Leonard, RN, PNP—coordinator
Valerie Castle, MD
Web site: description of U of Michigans Ped/Onc Late Effects Clinic

DeVos Children's Hospital
The After-Care and Transition (ACT) Program
Division of Pediatric Hematology/Oncology and Blood and Bone Marrow Transplantation
100 Michigan St, NE
Grand Rapids, MI 49503
Colleen Gardner and Tina Rodriguez are the nurse coordinators
Medical Director: Dr. David Freyer

(*Continued*)

Table 2. (*Continued*)

(616) 391-2238
Web site
The ACT clinic serves both children and adult survivors of childhood cancer. First visits to the ACT Clinic are being 5 years postdiagnosis and 2 years postcompletion of the last treatment regimen.

Minnesota

Fairview-University Children's Hospital
Long-Term Follow-up Clinic
Harvard St. and East River Rd.
Minneapolis, Minnesota 55455
Nancy Youngren—coordinator
To speak with Nancy Youngren please call 612-626-2140
Schedule an appointment: 612-625-5411
Joseph Neglia, MD and Daniel Mulrooney, MD
Web site: Long-Term Follow-up Study

Missouri

St. Louis Children's Hospital/Washington University School of Medicine
Late Effects Clinic
One Children's Place
St. Louis, MO 63110
Medical Directors: Robert Hayashi, MD; Shalini Shenoy, MD
For information or appointment call (314) 454-4240.
For children and young adults who are at least 2 years off therapy.

New Jersey

University Medical Center
Tomorrow's Children's Institution
Care and Beyond
385 Prospect Ave
Hackensack NJ 07601
(201) 487-8987
Hope Castoria, RN
Beverly Ryan, MD
Sees both child and adult survivors of pediatric cancer.

New York

Memorial Sloan Kettering Cancer Center
Long-Term Follow-up Clinic
Department of Pediatric Oncology
1275 York Ave
New York, NY 10021
212 639-8138
Charles Sklar, MD
Elaine Pottenger, MS RN CPNP
Web site: MSKCC Long-Term Follow-up Program
Sees survivors 30 years old or younger; will do one time consultation with older survivors.

University of Rochester Medial Center
Strong Children's Medical Center
Follow-up Clinic
601 Elmwood Ave.
Rochester NY 14642
585 275 2981
Cindy Proukou, RN, MSN, CPNP—coordinator
Andrea Hinkle, MD
Follows both child and adult survivors.

Roswell Park Cancer center
Long-Term Follow-up Project
Elm & Carlton
Buffalo NY 14263
Theresa Carbone MS RN CPNP—coordinator

Table 2. (*Continued*)

Daniel Green, MD
(716) 845-8011
Sees children, teens, and adults.
SUNI Upstate Medical University
KNOT: Kids Now Off Therapy
Pediatric Hematology/Oncology
750 E Adams St.
Syracuse NY 13210
315 464-7229
Sue Shaw, RN, MS, PNP—coordinator
Irene Cherrick, MD
Web site: description of the KNOT program
North Carolina
Duke University Medical Center
Pediatric Hem/Onc
Erwin Road
Durham, NC 27710 USA
919-684-3401 (appts for children and teens)
(919) 684-8964 (appts for adults)
Philip Rosoff, MD (children and teens)
Carlos DeCastro (adults)
Ohio
Children's Hospital Medical Center
ATP Five-Plus Clinic
333 Burnette Ave
Cinninnati, OH 45229
(513) 636-3512 Judy Correll—RN CPNP coordinator
Cynthia DeLaat, MD
Web site: description of and contacts for the ATP Five-Plus Clinic
Sees both child and adult survivors; will refer.
Akron Children's Hospital
START-UP clinic
"Staying Together After Recovery and Tapping Unlimited Potential."
One Perkins Square
Akron, OH 44308
Charlene Maxen, RN, CNP, CPON
Hematology/Oncology Nurse Manager
330-543-3215
Fax: 330-543-3836
Web site
Any childhood cancer survivor who has been off treatment for two years is eligible to participate in the START-UP program, regardless of age. The clinic usually meets only once a month but does plan additional clinics when students are off from school.
The Children's Hospital at the Cleveland Clinic
Pediatric Hematology/Oncology
9500 Euclid Ave.-Desk S-20
Cleveland, OH 44195
Office: 216-444-0015
Fax: 216-444-3577
Holly R. Kubaney, MSN, APRN, BC, Pediatric Nurse Practitioner
kubaneh@ccf.org
Greg Plautz, MD
The Center for Survivors of Childhood Cancer
Rainbow Babies & Children's Hospital
11100 Euclid Avenue
Cleveland, OH 44106
phone (216) 844-3070

(*Continued*)

Table 2. (*Continued*)

fax (216) 844-5431
e-mail: ChildhoodCancerSurvivors@uhhs.com
Web site
The clinic is held two times per month and we see children, teens and adult survivors of childhood cancer. All patients receive a summary of their cancer treatment, medical and psychosocial evaluation, screening and education about late effects, and referral and ancillary testing as needed.
Chad Jacobsen, MD (pediatric oncologist)
Catherine Peterson, PhD (psychologist)
Vicki Fisher, PNP (nurse practitioner).

<u>Pennsylvania</u>

Children's Hospital of Philadelphia
Long-Term Follow-up Clinic
34th & Civic Center Blvd
Philadelphia, PA 19401
215 590-3025
Wendy Hobbie-coordinator
Sue Ogle, CPNP and Barbara Anne, Heib CPNP
Jill Ginsberg, MD, Anna T. Meadows, MD
Sees both child and adult survivors.
Web site

Lance Armstrong Foundation Living Well After Cancer Program
The University of Pennsylvania Abramson Cancer Center
Linda A. Jacobs, PhD, RN
Director, The Lance Armstrong Foundation Living Well After Cancer Program
Abramson Cancer Center
University of Pennsylvania
Penn Tower Hotel #1428
3400 Spruce Street
Philadelphia, PA 19104
215-615-3371 (office)
Anna T. Meadows, MD
Adult cancer survivorship program and a transition program for adult survivors of childhood cancers.

<u>South Carolina</u>

Medical University of SC Children's Hospital
FACT (Follow-up after Cancer Treatment)
135 Rutledge Ave
PO Box 250558
Charleston SC 29425
843-792-2957
Diane Dufour, MS, CPNP—coordinator
Sonja Muckensuss, RN, BSN
Julio Barredo, MD

Children's Medical Center of Dallas
After the Cancer Experience (ACE)
1935 Motor Street
Dallas TX 75235-7794
(214) 456-2948, Fax (214) 456-2948
Coordinator: Debra Eshelman, RN, CPNP
Gail Tomlinson, MD, PhD (children and teens)
Kevin Oeffinger, MD (young adults)
Web site: description of the ACE program

MD Anderson Cancer Center
Long Term Survivor Clinic
1515 Holcombe, Box 87
Houston Tx 77030
713 792-6619
Nita Burrer RN, ANP, CNS—coordinator

Table 2. (*Continued*)

Norman Jaffe, MD
Steve Culbert, MD
Web site: good description of the long-term survivor clinic
Sees children, teens, and adult survivors of childhood cacner.

Texas Children's Hospital
Late Effects Clinic
Hematology/Oncology
6621 Fannin St.
CC-1510.21
Houston Tx 77030
832 822-4727
Coordinator: Gaye Hamor, MSHA
Social worker: Amy Waltz
Family Nurse Practitioner: Jennifer Lin
Jo Ann Dreyer, MD
Sarah Bottomley, CPNP
ZoAnn Dreyer, MD
Web site: good description and contacts for the long-term survivor clinic

Cook Children's Medical Center
Life After Cancer Program at the Hematology & Oncology Center
901 Seventh Avenue, Suite 220
Fort Worth, Texas 76104
(817) 810-2125
Lisa Bashore, MS RN CPNP
Jeffrey C. Murray, M.D.
Web site: description on the hem/onc page
Treats up to age 30 and will refer adults.

The Lance Armstrong Foundation and Cook Children's Medical Center in Fort Worth are partners in the Life After Cancer program.

<u>Washington</u>

Children's Hospital & Regional Medical Center
Division of Hematology/Oncology Mailstop B-6553
ACCESS Long-Term Follow-up Program
4800 Sand Point Way NE, B-6553
Seattle, WA 98105
(206) 987-2106
Debra Friedman, MD
Karen Wilkinson, ARNP

<u>Washington, D.C.</u>

Long Term Survivor Clinic
Department of Hematology-Oncology
Children's National Medical Center
111 Michigan Ave., NW
Washington, DC 20010
Appts: 202-884-2140
Nurse Coordinator: 202-884-3568
Medical Director: Gregory H. Reaman, MD
Nurse Coordinator: Revonda B. Mosher, RN, MSN, CPNP

<u>Wisconsin</u>

University of Wisconsin Hospital and Clinics
Caring for Life Clinic
600 Highland Ave.
Madison, WI 53792
(608) 263-6200
Peggy Possin—coordinator
Diane Puccetti, MD

(*Continued*)

Table 2. (*Continued*)

Children's Hospital of Wisconsin
Oncology and Bone Marrow Transplant Long-Term Follow-up Clinic
8 East Clinic
9000 W. Wisconsin Ave
Milwaukee, WI 53226
Phone: 414-266-2420.
Contacts: Deb Schmidt, RN, MSN, CPNP-Oncology
Lynnette Anderson, RN, MSN, CPNP- BMT
Web site
Treats children, adolescents and young adults.

in their institution. This requires the philosophical and financial support of the institution.

The LAF has recently taken the lead in the funding and development of the first adult survivorship program Network across the country. In addition to the LAF LWAC Program at Penn, over the last two years the LAF funded the Dana Farber Cancer Institute and Memorial Sloan Kettering Cancer Center to develop adult cancer survivorship programs, and these programs are currently in the development phase. In the summer of 2005 the LAF invited select NCI-designated cancer centers to submit applications for funding to develop adult cancer survivorship programs at their institutions. Three additional centers were funded by the LAF and over the next 5 years these centers as well as the already funded LAF programs will work together under the guidance of the LAF as a Network of adult cancer survivorship centers that will collaborate on the development of clinical care programs and research projects to explore and meet the needs of the growing population of adult cancer survivors. The cancer survivorship focused work of the LAF is unparalleled as we move forward with this national agenda.

A better understanding of the late effects of cancer treatment comes from the growing research in this area as well as from survivors who are identifying problems and seeking appropriate providers for managing these challenges. The late effects of cancer treatment have been under-recognized and consequently under-treated. For the most part, providers are not adequately prepared to recognize and manage late effects, and few providers screen for late effects of treatment despite knowledge of potential problems caused by surgery as well as treatment with chemotherapy and radiation therapy. The LAF Network of survivorship centers across the country will collaborate with ASCO, the American Cancer Society, the Centers for Disease Control, the Oncology Nursing Society, the National Coalition of Cancer Survivors and other groups to work toward meeting the National agenda by standardizing follow-up care and meeting the broad spectrum of unmet needs of adult cancer survivors.

REFERENCES

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Part IV

Survivor and Provider Perspectives

Chapter 23

Survivor Perspectives on Quality Care

Kathryn McPherson and Rod MacLeod

1.0. INTRODUCTION

Understanding what constitutes "quality" is complex. This seems a particular issue in conditions like cancer because they are themselves complex, being variable in nature, presentation, and outcome. Some would argue that we have in fact failed to ask some of the key questions that would really help us develop our understanding of what comprises quality, instead making "health professional" assumptions and therefore ending up somewhat errant in the conclusions we have tended to reach.

An inescapable tension in discussing quality is that the different parties involved (funders, providers, consumers, and taxpayers) may have quite different needs and aims.[1] Whilst each of these groups would probably agree that they want the best quality services that can be provided within the resources available, the extent to which they agree on what those components are is frequently less clearly articulated. It may be that understanding this "different-ness" is important in itself (in that some quality components will be more or less relevant to different parties) but also crucial if we are to recognize the strengths and limitations of specific service evaluations.

This chapter sets out to explore how quality in cancer care may be viewed, focusing in particular on how a better understanding of patient/client and family perspectives can contribute to responsive and high-quality service development and delivery for cancer survivors.

2.0. MODELS OF QUALITY

We first present an outline of theoretical models in quality of health care. By doing so we aim not just to add to the "rhetoric" about quality, but to stimulate some thought about issues that are important and yet sometimes overlooked.

2.1. Seven Pillars Of Quality

Avedis Donabedian who might be considered the "father" of quality, described a model of understanding "quality" in health services incorporating the structure, process, and outcomes of the service[2] where

(a) *Structure* encompasses the characteristics of medical care that are relatively unchanging i.e., the materials and manpower available for care.
(b) *Process* addresses the content of that care, i.e., how the patient was moved through and out of the health care system and the services that were provided during the care episode.
(c) *Outcome* pertains to the impacts or results of that care.

In his original work, it is clear that Donabedian equated quality with effectiveness i.e., the outcome of the most importance was the measurable impact of a service or intervention with effectiveness of services usually including concepts relating to

> . . . having the organisation meet the citizens' requirements and having a programme or activity achieve its established goals or intended aims.[3]

Donabedian argues that in order to achieve effectiveness, it is crucial for the right structures to be determined from research studies and implemented, and that process needs to be considered principally when adverse outcomes are being investigated. His later writing in this area enlarges the original structure–process–outcomes–framework to become the "seven pillars of quality"[4] which include both efficiency (defined as the cost for any given improvement in health) and optimality (the best compromise between health benefits and cost). He also includes three attributes with a patient focus: acceptability, legitimacy, and equity. Although he believes that the pursuit of each of the several attributes of quality can be mutually reinforcing, as when effective care is also usually more acceptable and more legitimate, he accepts the pursuit of one attribute may be in conflict with the pursuit of others, and that some sort of a balance is required. This notion of potential conflict within quality is crucial and Donabedian's work offers some practical ways to conceptualize this conflict and as such, provides a framework for moving forward.

2.2. The World Health Organisation

The World Health Organisation (WHO) has recently proposed a framework for the assessment of performance of national health systems[5] with "performance" approximating the "optimality" of Donabedian. The WHO Report carefully avoids use of the word "quality" but is clearly interested in similar aspects of systems/services as Donabedian with the assessment of performance based on the overall attainment (effectiveness) of the system relative to the resources (structures) available. Attainment has two components: "good health" measured simply as disability adjusted life expectancy (DALE) as well as a "fairness" component which tries to adjust for variations in the distribution of good health. In essence, the WHO approaches attempts to measure, standardize, and compare effectiveness and efficiency for different health systems.

2.3. Operationalizing Quality

In addition to the approach adopted by WHO, others have attempted to operationalize quality and performance generally using "quality indicators."[6–8] However, these indicators tend to be arbitrarily assigned and relate more to ease of measurement than any evidence that they reflect underlying quality (or lack of it). In addition, outcomes using these indicators are often difficult to interpret as they depend on an innately predictable system, something that many argue is just not cancer care. A recent US report "Crossing the quality chasm"[9] concluded that rather than using rigid blueprints, we might be better to focus on a "good enough vision" of quality. The six aims that make up this "good enough vision" are greatly reminiscent of Donabedian's early work: that services be Safe, Effective, Patient Centred, Timely, Efficient, and Equitable. Such aims and the accompanying rules by which to achieve them (Table 1) seem far removed from a focus on what sometimes seem more "mechanistic" approach to quality indicators we often observe in health care settings and review.

Despite what Kelley and Tucci[8] suggest to be valiant efforts in this report to help the United States reconsider its direction in delivering "quality" health care services, they comment that the report is written from a perspective that does not seem to embody the diversity of view on these rules that actually exists within even the provider community. Indeed, they go so far as to suggest that

> Despite rhetoric to the contrary, American health care remains a cottage industry, where providers are preoccupied with financial survival and the challenges of regulation and litigation. They are driven by highly individualised needs, not an abstract or common desire to improve health care.[8]

We would probably like to think that this sort of comment is not applicable to the health services we contribute to or organize, whether in the USA or elsewhere. However, it is salutary to consider than a mismatch between the "talk" and "actuality" might prevail in many more services than we would like, even just because of competition for funding.[10–12] It also seems vital that we should be at pains to avoid a situation where practitioners become increasingly concerned about safe practice in order to avoid punitive action, rather than to enhance quality, as this motivation itself may be a risk to quality.[13,14]

There are clearly varying views, even just within providers, regarding the different components of models proposed. Different attributes of quality are therefore

Table 1. Ten Rules for Achieving Quality Services

1. Care based on continuous healing relationships
2. Customization based on patient needs and values
3. The patient as the source of control
4. Shared knowledge and the free flow of information
5. Evidence-based decision making
6. Evidence as a system property
7. The need for transparency
8. Anticipation of needs
9. Continuous decrease of waste
10. Co-operation among clinicians

Committee on Quality of Health Care in America 2001.[9]

likely to be more or less relevant to each of the other stakeholders. Furthermore, attempts to measure particular attributes such as effectiveness for example, are necessarily informed by the perspective of the group doing, or requiring, the measurement.

3.0. CONSUMER'S PERSPECTIVES OF QUALITY HEALTH CARE

Having argued the case that different stakeholders will have different views about what comprises good quality care, our brief here is to focus particularly on what users of cancer services can tell us about quality.

It would seem surprising if consumers did not wish to be managed in services with features that are associated with best outcomes, frequently fitting the medical provider perspective on quality. However, in depth interviews that we have carried out with people with life threatening and other chronic conditions[15–17] suggest that current models outlining the consequences of many conditions, may be missing the mark, at least in part. Further, issues of access, involvement in decision making, cultural considerations as well as the nature of the surroundings may all play a part in how patients and their families assess the quality of services we provide.

A possible reason for the mismatch between what we (as health care experts) think is important to patients, and what they (as a different sort of expert in their own condition) actually regard as important, may well be related to failing to ask them or not giving full credence to their view even if we do ask.[18] This is not a pedantic point about language or semantics as it is hardly remarkable that we may be missing out on what are the key quality indicators for this important stakeholder. Certainly, it would suggest that it might be premature to adopt models of quality that call for "customisation based on patient needs and values" and "the patient as the source of control" without fully understanding what that means. Whichever way one looks at it, quality in cancer care must be a multidimensional concept and those dimensions should include the views of the consumers.

As identified in Section 2, many facets of care need to be addressed if we are to be certain of good quality care including relevance of that care.[19] It is not hard to see a place in that list for the views of Black who would add humanity (if ever that can be measured).[20] Vardy and Tannock[21] in their comprehensive review of the area identified three particular points of relevance. Firstly, is the right treatment being given? Secondly, is it being done well? Thirdly, is the patient being treated in addition to the disease? Part of the problem of evaluating cancer care is that historically such evaluation relates predominantly to clinical outcomes with "evidence" for high-quality care coming principally from large randomized control trials. The issue is that these may miss some of the core concepts of high quality from the regular consumer's perspective, given the tight selection criteria of patients involved in trials and the application of treatment under ideal conditions which may influence the outcomes of such studies.

However, it is fair to say that the quality of evidence for quality cancer care tends to be judged according to the robustness of that evidence: how the trial was designed, executed, and analyzed and secondly, external factors such as concordance with results of related studies. Commonly, end points in cancer trials and therefore an end point in evaluation of cancer care are tumor response, survival, and improvements in quality of life (QOL). Improvements in symptom control and/or QOL are often seen as major areas of interest for cancer survivors and the calls for a greater focus on these outcomes is rightly made.[22] However, there is also a growing awareness that expert-derived outcome measures, and interventions directed at achieving these outcomes, may have limited relevance to people with cancer, particularly to terminally ill people.[23]

One paper we mentioned previously[16] highlighted the growing recognition that cancer outcome measures, such as many of the QOL tools, may have limited validity in assessing patients' experiences and responses to care. These authors identified a central concern of consumers of such services, "taking charge" which is not clearly addressed in existing QOL measures; they also, incidentally identified that whilst preserving dignity was important, it was not commonly considered an 'ultimate' goal from a patient perspective. Whilst these findings were derived from a qualitative study involving people at the end of life they do have relevance for important outcomes for people who are undergoing cancer treatment and those who are longer term cancer survivors.

Much of the evaluation of the quality of cancer care then is dependant on the way in which the treatment is delivered. The National Cancer Institute (NCI) in the United States developed a project in 2002 entitled the "Cancer Quality of Care Measures Project."[24] This project is intended to capitalize on an innovative approach for bringing public and private parties together to create "voluntary consensus standards" for decisions bearing on health care quality. As part of the study they will adapt the National Quality Forum Strategic Framework Board's report to cancer care quality and assess the state of the science of cancer quality measurement. The first phase of this project was to look at cancer site-specific measures (breast, colorectal, and prostate cancer diagnosis and treatment). The second area of phase one was to look at cross-cutting measures applied to multiple possible cancer sites involving access (including clinical trials and culturally competent care), communication and co-ordination of care, and prevention and screening within the health care system. They also looked at symptom management and end of life care. Phase two of the study which began in 2004, conducted evidence-based reviews of available measures of cancer quality to identify measures that are ready for use. It also planned to chart strategies for developing and testing new measures. This innovation from the NCI is still a long way from completion but it gives an indication of the relatively early stages of our understanding of evaluating quality of care, far less including the focus of consumers of that care explicitly in such evaluation.

Early in 2005 the National Quality Forum (NQF—at www.qualityforum.org) announced its endorsement of a standardized survey of patients' perceptions of their experience of hospital care. The survey instrument is a 27-item survey designed and developed over 3 years by groups including providers of care and consumers. It includes questions addressing seven domains of hospital care which are all relevant to cancer care: communication and responsiveness of hospital staff, pain control, communication about medicines, the environment, and discharge information. The NQF also has as a goal, to develop a standardized framework for the selection and implementation of quality measures and also to establish overarching principles for an ideal measure set that can assess the totality of cancer care and serve as a guide for the development of new measures. One of the purposes is to identify opportunities to improve cancer care in order to reduce death, disability suffering, and the economic burden caused by cancer—very similar goals to the Cancer Control Strategy published in New Zealand.[25] The goals of the New Zealand Cancer Control Strategy (as influenced by the Australian National Cancer Control Initiative and the Canadian Strategy for Cancer Control and informed by consumer views) are to:

- reduce the incidence of cancer through primary prevention
- ensure effective screening and early detection to reduce cancer incidence and mortality
- ensure effective diagnosis and treatment to reduce cancer morbidity and mortality
- improve the QOL for those with cancer, their family, and whanau through support, rehabilitation, and palliative care
- improve the delivery of services across the continuum of cancer control through effective planning, co-ordination and integration of resources and activity, monitoring, and evaluation
- improve the effectiveness of cancer control in New Zealand through research and surveillance.

Within the USA, the National Coalition for Cancer Survivorship (NCCS) has been similarly active in calling for key principles to underpin cancer care. In particular, the NCCS highlighted survivorship to be a distinct phase of the trajectory of cancer care as enduring consequences of cancer may well remain even in the absence of active disease. Indeed, cancer survivors have been shown in a large cohort study to have poorer health outcomes than matched control individuals without cancer.[26] This point is a crucial reminder that although frequently considered separate fields of practice, integration of "rehabilitation" into cancer care may well be an additional requirement for many survivors. This point is further pursued in a recent exploration of cancer care for survivors[27] with cancer being clearly many things, including now for many people, a chronic condition.

Within the United Kingdom, attempts to improve cancer services led to the NHS Cancer Plan[28] but progress in terms of actual operations has fallen behind what was expected to date. The Cancer Plan provides a detailed account of the UK government's national programme for investment in, and reform of, cancer services in England. It aims to reduce death rates and improve prospects of survival and QOL for cancer patients. The Plan aimed to "guarantee" high-quality treatment and care throughout the country facilitated by the development of cancer networks which include the voices of consumers in their planning. The core goals of improving prevention, promoting early detection, and effective screening practice were thus influenced by consumer views on how best to achieve such improvement. However, by the end of 2005, 30% of networks visited by the National Audit Office did not have comprehensive plans for providing cancer services in their locality.[29] Of particular concern is that patients are diagnosed with cancer at a later stage in the United Kingdom than in other European countries. As in other countries such as the United States this can particularly affect people from deprived areas. Facilitating access to screening and diagnostic services requires that patients have more (but also more appropriate) information to understand the referral processes and an increased understanding of warning signs and symptoms of cancer. The Expert Patient Program and its contribution to enhancing the appropriate information will be discussed in more detail in Chapter 27.

Despite what appears increasingly good intentions of delivering quality care for cancer survivors, research indicates huge room for improvement. There are many studies which indicate that patients leave consultations confused about their ongoing diagnosis and prognosis and uncertain of the management plan and intended treatment.[30] However, communication skills can be taught and considerable improvements can be made in the doctor/patient relationship and hence in the perception in the quality of care provided.[31–33] There are studies[34] that highlight some good elements of communication such as friendliness, a caring demeanor, and clarity of information. Others, from a patient and/or family members' perspective suggest that the areas of the greatest need after receiving a diagnosis of cancer are: care availability and quality of disease management; good information; sympathetic communication; and most importantly regaining control of their lives.[16,35–37] High quality cancer care for many would suggest an involvement in decision making on the part of the patient and their family but sadly this is not yet seen as the norm[38] and most cancer patients fail to achieve their desired level of involvement in treatment decision making.[27]

There are other initiatives in the United Kingdom which may lead to an improved consumer involvement in elements of cancer care. INVOLVE (http://www.invo.org.uk) is a national advisory Group, funded by the Department of Health, which aims to promote and support active public involvement in the National Health Service, public health, and social care research. They believe that involving members of the public leads to research that is more relevant to people's needs and concerns, more reliable and more likely to be used. CancerVOICES http://www.cancervoices.org.uk. is another organization in the United Kingdom which may help to shape the future of cancer care in that country. These groups provide local and national feedback on the levels and nature of service provided in cancer care. They are supported by a charity organization, the Macmillan Cancer Relief.

4.0. CONSUMER VIEWS ON "CARE"

Having considered what consumers view as contributing to quality care (and the deficits therein) it seems rather important to touch upon the role of "care" itself. The nature of care in the delivery of health services is variable amongst the professions and therefore, almost by necessity, has variable meaning amongst those receiving care. For many, the expectations of care are centered on the technical expertise and skill with pharmaceutical agents to "make well" again. Caring has behavioral and motivational elements[39]—it has physical manifestations but also psychological, spiritual, and social dimensions. Even in studies carried out in the early days of the technological revolution in health care, people with cancer, when asked to assess their perceptions of caring behaviors of nurses, consistently ranked the highest caring behaviors as those that showed competence and knowledgeable technical skills and abilities.[40] Conversely when the same tool was used to measure cancer nurses perceptions of what *they* thought would make the patient feel cared for the nurses' ranked expressive humanistic behaviors highest—listening, comforting, and expressing sensitivity.[41] Clearly the person being cared for will have differing needs as the illness changes or progresses, the need to be physically cared for may be greater at times and care for the physical body giving health care professionals an opportunity to introduce the concept of spiritual or psychological care with varying degrees of intimacy. Nurses speak of the ability to foster or engender hope in their caring practices[42] but it is at an individual level that we need to ensure we understand the patient's need for care. Larsson *et al.* have compared cancer patients' and staff perceptions of caring behaviors[43] showing that patients rate the health professional's ability to anticipate needs as the highest ranking characteristic whereas the carers ranked the provision of "comfort" as the highest.

Overall, a review of the available literature would suggest that patients value a high level of competency and skills as caring characteristics but staff value the interpersonal aspects of the relationship with the patient. Those people who are acutely ill would perhaps focus on the immediate tasks and treatments provided (giving the right medication for pain at the right time for example) if their survivorship is not long lasting, or in fact moves to a more long term care situation, the patient may be more focused on a closer, more meaningful relationship.[44] One thing that can never be emphasized enough is that all patients need doctors and nurses who care as well as cure—this is an ever more difficult task for medical educators as the advances in clinical practice threaten to engulf the undergraduate curricula[45] but those humanistic elements of care must never be lost in our evermore sophisticated world of technical medical practice.

5.0. IMPLICATIONS AND RECOMMENDATIONS

We have outlined above a number of factors that are likely to contribute to difficulty in addressing "quality" of health care in cancer survivorship. One way of reducing the tensions that exist between the needs of funders, providers, and consumers of heath services is to make explicit the components of quality that are of interest to the various parties. In order to do this satisfactorily, the debate must utilize (and expand as required) theoretical models that provide a way of considering quality issues. Knowledge about cancer survivor perspectives on quality care is growing but it is early days. Focused attention on that perspective utilizing appropriate methodologies is likely to help us prioritize resource allocation toward higher quality and more responsive services for cancer survivors. Facilitating the survivor voice to be heard and to impact on service development will mean that effort in audit and evaluation will be worthwhile and not just a matter of ticking boxes.

6.0. SUMMARY

What is meant by "quality" of health care, and how we set about achieving it is a longstanding and somewhat fraught topic of discussion. Confusion and conflict about what might truly comprise "quality" and its related components exist, with some suspecting developments to be more frequently driven by political rhetoric than the needs of patients and their families. Whilst some confusion is perhaps unavoidable given that the technical language regarding quality is itself complex, it seems there are identifiable sources of conflict that we can confront and address to truly achieve better quality care. This chapter has argued that a potential source of conflict arises from the fact that there are different interested parties in health care and as such, potentially quite dissimilar views that might need to be addressed. In particular, we refer to research which explores the patient's view of "what matters most" in cancer care and survivorship. Theoretical models of quality are also explored to provide a context for discussing these issues and possible ways forward. We also examine what consumers have to say about "caring" itself as a component of health service delivery. The chapter presents an argument that improving the development and delivery of quality of cancer services in ways that are meaningful rests upon a better understanding of patient perspectives.

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Chapter 24

Living with Advanced Cancer

Sheila Payne

1.0. INTRODUCTION

Cancer is changing: both the image that is presented in the media and the way people with the disease and their families construe it. There has been a remarkable growth in optimism associated with cancer and this is largely due to the numbers of people surviving with their disease. While cancer remains associated with increased risk of morbidity and mortality especially for those living in developing countries, many patients fully recover. However, there remains some ambiguity and uncertainty around survivorship because as well as complete cure, it can also mean periods of disease-free remission but eventual recurrence. A minority of people with cancer live with advanced disease for sometime before they die and it is this group that will be the focus of the current chapter. All of these cases are now considered under the general category of cancer survivor.

Data from Cancer Research UK[1] indicate that more middle aged people with cancer are surviving, as in the last decade deaths in those people aged 35–69 fell by 18% in men and 17.3% in women. Certain types of cancer mortality have demonstrated even greater falls, for example, the number of people dying from bowel cancer has dropped by 22% in men and 26% in women, stomach cancer by 39% in men and 45% in women, and in women breast cancer deaths have fallen by 25% and cervical cancer by 33%. In the USA,[2] over 95% of women diagnosed with localized breast cancer and over 75% with regional spread are anticipated to survive for 5 years. This reduction in mortality can be attributed to improvements in cancer screening, earlier diagnosis, better treatment, changes in food preservation, a steady decline in smoking particularly in men and other public health measures. During the same period the incidence of the common cancers such as lung, breast, bowel, and prostate cancer are largely unchanged so the implication is that more people are living for longer periods of time with their disease.

Living with the unpredictable nature of disease recurrence and the uncertainty of remission and subsequent relapse is the focus of this chapter. Medical advances mean that increasing numbers of cancer patients experience prolonged periods when they are aware of their advanced disease. Paradoxically while some medical interventions have achieved increased survival, they have also prolonged awareness of dying for certain cancer patients. Potentially curative and palliative treatments may be given concurrently although this may be dependent upon the health care system in which patients are provided with care. There are differences in US and UK models of hospice and other end of life and palliative care services. Typically in the US where hospice programs require patients to relinquish curative treatment, referral is delayed until the last days or weeks of life.[3] In the UK, specialist palliative care services and hospices may provide services concurrently with other health care providers.[4] This chapter is concerned with exploring how patients with cancer and their families cope with recurrence. It also aims to examine how health and social care services seek to prepare and support patients and families facing suffering associated with their disease and its treatment, and how they deal with the lasting health impairments and disabilities that they may have to confront.

The chapter will introduce some of the theoretical and empirical literature on coping with loss, change and uncertainty. These will be discussed within the context of a public health agenda, which recognizes that for many cancer patients, survivorship means living with the long-term consequences of treatments and potential recurrence. The impact of this upon role functioning and their sense of self will be explored drawing upon sociological and anthropological research. It will also draw on accounts produced by cancer patients themselves when living with the realization of their impending death. These will be compared and contrasted with the accounts generated by health professionals in their visions of what living with advanced cancer must be like. Finally, living with advanced cancer impacts on social relationships; so the last section will discuss the implications for families and carers.

2.0. LIVING WITH ADVANCED CANCER

Living with advanced cancer challenges people's concepts of identity and personhood. The sociological and anthropological literature[5,6] has long emphasized the changes brought about by illness and contact with health care services, to personal identity, role and feelings of competence as a person. While early functionalist accounts[7] of the patient role have been heavily critiqued[8] and are now largely discounted, there remain a few elements that are highly salient for consideration in this chapter. The use of the social label "patient" continues to be dominant in the language of health care workers, health care managers and policy makers, and is widely used by the public. It serves to differentiate the "well" from the "ill," the "cared for" from the "care workers." It is a social role with its own set of expectations, responsibilities and constraints. Arguably the term "cancer patient" has also developed a specific set of socially defined attributes and expectations.[9]

Cancer survivors have to simultaneously inhabit the world of the "healthy" population and the world of the "patient," when they undergo medical surveillance procedures like scans and clinic check-ups. While for some patients regular follow-up examinations are reassuring, they also serve to raise awareness of their vulnerable status as "cancer patients" and exposure to the presence of other cancer patients who may be fairing worse than themselves in clinics.[10] Paradoxically having no treatment but being subjected to regular medical surveillance may also be very alarming. For example, "watchful waiting" which is the medical term applied to surveillance when a person does not receive immediate adjuvant treatment such as chemotherapy or radiotherapy following surgery, could be assumed to be less stressful and distressing than active invasive treatment. However, a study comparing outcomes for men with stage 1 testicular teratomas indicates that the uncertainty and the need for regular medical surveillance may be more likely to result in raised anxiety than those treated by chemotherapy.[11] The researchers explain this finding in terms of the greater availability of feedback and "safety signals" provided by health care staff in those men undergoing chemotherapy.

3.0. UNDERSTANDING HEALTH, ILLNESS, AND UNCERTAINTY

It is important to make the distinction between *illness* which refers to the subjective experience of being unwell and may or may not be linked to an organic disease, and *disease* which refers to a recognized pathological state. It is therefore possible for a person to have a life-threatening disease and to describe themselves as "well." Likewise, it is also possible for a person to feel ill but not have a disease. The recognition and labelling of disease states (diagnosis) has traditionally been the role of medicine. A diagnostic label takes no account of the meaning a person places on their symptoms. The literature on illness representations[12,13] suggests that people need to acquire certain information (not necessarily from health professionals) to understand the cause, timeline, severity, duration, and cure of their illness. Inability to address any of these elements tends to provoke continuing anxiety and discomfort. For example, it is often difficult or impossible for people to attribute a cause to their cancer, or if they do, it may involve elements of self-blame such as by smokers. A framework for understanding uncertainty in illness was proposed[14–16] where aspects of illnesses, treatments or events associated with illness are inconsistent, random, unpredictable, overly complex or where information is lacking, these are likely to provoke feelings of uncertainty. Many of these features are present for cancer survivors. For example, the possibility of recurrence remains a threat which is unpredictable. In those with advanced disease, there is the uncertainty of dying. Wright and Flemons[17] described seven categories along a continuum from living to dying where "patients found themselves simultaneously hanging on to life and reaching out to death (p. 266)":

- Imprisoned by death
- Carpe Diem (Seize the Day)
- Carpe Mortem (Seize the Death)
- Knowing the enemy
- Life and death transformed
- Silenced by death
- Waiting for death

Typically, life-threatening cancer changes the outlook of the person and alters the possibilities available to them and their families. The taken-for-grantedness of life and the expectation of a (almost) limitless future diminish. With increasing physical and/or mental decline come unwelcome changes such as social isolation as treasured roles are modified and eventually relinquished. Generally, life-threatening illnesses are marked by a transition from activity to passivity. There may be an incremental dismantling of essential features of personhood, such as the appearance of the body for example in cachexia, or changes in cognitive and emotional capacities in those with end stage brain tumors. This may result in a withdrawal of social relationships as in the social death described by Sudnow.[18]

When living with advanced cancer, patients need help in establishing whether their symptoms are transitory or if they are permanent. They also need help in distinguishing the causes of symptoms as similar symptoms may be construed as indicative of recurrence, a new cancer, a minor illness, a comorbidity or "normal" aspects of ageing. The continual uncertainty about the possibility of recurrence may gain greater salience during clinic check-ups or following a media story or when encountering the experience of a fellow patient. Such uncertainty may cause feelings of a loss of control over the person's body and life, and less feelings of security in other aspects of their life. It may be difficult for older people to discriminate between anticipated changes attributable to ageing and those of recurrence. Responses may vary from hyper-vigilance, for example, by daily checking for the presence of breast lumps, to a fatalistic disregard for all symptoms. Negotiating a comfortable middle ground in which possible suspicious symptoms are drawn to medical attention, but life is not dominated by these concerns, is difficult for some patients to achieve. This area of concern could benefit from more definitive research so we can provide information that is more evidence based. Currently, we do not know many of the answers to these major questions.

One of the most prevalent symptoms is fatigue which may be caused by the disease process and/or treatments such as radiotherapy.[19] While fatigue is common within the general population, the extent and depth of the tiredness may be so severe as to compromise normal everyday life, employment, and social relationships. A number of interventions originally developed for people with chronic fatigue syndrome may be potentially useful. These usually involve self-management strategies including graded exercise, planned rest and careful pacing of activities to prevent cycles of over-exertion followed by collapse.[20] These may be useful to cancer survivors who are concerned about over-tiring themselves and precipitating further illness.

4.0. CHANGING APPEARANCE

Psychological research[21] and evidence from the popular media show that appearance matters. Western societies are heavily influenced by common norms which value physical appearance that is younger, attractive, slimmer, and without visible difference or disfigurement. Arguably stereotypical images of fashion models or celebrities are not normal; they are often enhanced by special clothing, make up, exercise and dietary regimes, and cosmetic surgery. But these are the physiques to which many people aspire. The individual impact of unwelcome changes to appearance is the outcome of an interaction between personal values, social and gender norms, social context and expectations. For example, an older man with alopecia from chemotherapy who has previously always worn a beard and regards this as part of his naval identity may be more distressed than a young man with similar hair loss whose mates may shave their heads. The actual type of physical difference does not predict the extent of distress or acceptance. There is a considerable literature in cancer nursing which focuses on body image changes,[22–24] but more recent research suggests that individual appraisal and meaning of bodily differences influence expectations and interactions with others in social encounters to a greater extent than formerly realized.[21] Some people experience great disturbance from changes to their physical appearance and lose their sense of identity.

Lawler[23,24] has emphasized that the outward presentation of the body has become very influential in defining identity, individuality, and conveys powerful messages about culture. For example, our choice of clothing and accessories signify wealth, religion, age, and gender. Likewise, body art like tattooing and inserting ear rings or nose studs are closely linked with the way we wish to convey both our identity as cultural group members and individual identity. Wearing make up and styling hair in certain ways are gender markers in most societies. The failure to maintain usual standards of personal dress and grooming may be profoundly difficult for some people with advanced cancer. For example, the thinness associated with cachexia or the swelling arising from ascites may be difficult to mask by clothing and may lead people and their families to feel depersonalized by the experience of illness.

For those living with advanced cancer, personal appearance may have been permanently changed by treatment effects such as surgery which removes visible body parts such as the breast, or altered body contours. Surgery and radiotherapy may result in permanent scarring, restriction of movement and loss of function. Body parts may become swollen and dysfunctional such as with lymphoedema or ascities. Side effects such as lymphoedema following axillary node dissection, is a relatively common and difficult to treat outcome of surgery and radiotherapy for breast cancer. Pervasive changes in skin quality, muscle tone, and sexual function may result from induced early menopause. Depending upon the location and nature of the cancer, advanced tumors may result in fungating wounds or fistulae with major problems in medical management, odor, and infection. In addition, advanced cancer may be marked by cachexia which causes an emaciated appearance and frailty.

Some patients may be faced with temporary or fluctuating changes to physical appearance which may be no less distressing than permanent ones. Perhaps the best known and most researched are the effects of hair loss resulting from cancer chemotherapy. There are a number of moving accounts of the experience of hair loss, and attempts to conceal the loss using wigs, hats and scarves. Even when the hair regrows it may be a different color or texture from the original hair. Other changes to appearance may result from the side effects of pharmacological therapies such as steroids, with weight loss or gain, and a redistribution of body fat. People with cancer may use a number of strategies to adapt to changes in physical appearance including camouflage with specialist make-up, wigs and prosthesis, but these may be uncomfortable or ineffective. Alternatively, some people choose to acknowledge their changes and celebrate their difference. The careful selection and design of clothing may enhance well-being and minimize the visible impact of altered appearance as described in Textbox 1.

Textbox 1. A Fashion Project for Women with Advanced Cancer[25]

Staff and volunteers at St Christopher's Hospice, London, UK collaborated with students attending the London College of Fashion in developing a special project for five women with advanced cancer. The aim of the project was to help these women to come to terms with the changes in physical appearance wrought by their disease and to celebrate their personal beauty. It arose out of the wishes of the patients to have more suitable clothing than could be found in the shops. Over six weeks the project team worked with the women to design comfortable and flattering garments, choose fabrics and colors to their tastes. The clothing was tailored to their shapes and sizes by the volunteers. The patients visited the London College of Fashion to learn more about the production process. Finally a "fashion show" was organised at the hospice chapel where the woman bravely and proudly paraded their new clothing in front of family and friends. The women reported that despite feeling tired and experiencing the adverse effects of their disease and treatment they felt transformed by this project and beautiful.

5.0. SOCIAL ROLE AND IDENTITY

The next section will consider the theoretical and empirical literature on coping with loss, change, and uncertainty. There will be a focus on psychological models of coping and a discussion of their strengths and weaknesses. Most models of coping are derived from social cognitive theories and suggest that decision-making in health care contexts are largely based on individual factors such as personality and cognitive processes. Instead I will also draw upon applied psychological theorizing and critiques drawn from health psychology to argue that more social, cultural, and community-based understandings are required to explain how patients manage their advanced disease. This section will also consider theoretical models of the "self" in illness and disease drawn from sociology and anthropology.[26–28]

Psychological approaches to questions of self and identity fall into four major groups; psychoanalytic and psychodynamic therapists have drawn upon their clinical work,[29] humanistic psychologists have drawn upon insights from psychotherapeutic work,[30–32] social psychologists have used experimental methods,[33] and more recently social constructivist theorists have drawn upon narrative methods.[34,35] Sociological approaches have tended to emphasize the influence of historical, cultural, and economic circumstances.[8] Identity was believed to be predominantly derived from one's social position at birth (e.g., being born to wealthy or poor parents), and acquired through education and employment. Identity was also acquired from performance of social roles like being a parent, a widower or widow. These determine to some extent what are regarded as appropriate behaviors and ways of interacting with others. More recently, identity has been thought of as a more flexible and negotiated construct. It has also been suggested that people living in contemporary western societies take a more reflexive and internalized position on identity.[36] Taylor[36] argues that in many countries people now spend more time pondering upon existential and other questions about the meaning of life and their role in it, because there is less acceptance of broad frameworks like religion. This is reflected in the position taken by Giddens[37] who suggests that social structures do not merely influence a person's self-identity but are manifest through their engagement with social practices. He argues that in modern society, identity is usually not fixed but is constantly renegotiated throughout the life span.

In the context of advanced cancer, people are often in the ambiguous situation of trying to lead "normal" lives but also engage in disease self-management strategies such as dietary modifications, skin, wound or stoma care regimes. The way that these are incorporated in personal habits and family routines may determine the pattern of adherence to health care advice. For example, painful mouth ulceration and lack of taste may mean that special food has to be prepared or that smaller portions are consumed which marks the person with cancer as different. Cancer survivors at this stage may be intolerant of specific foods, flavorings, spices or temperatures. These factors may compromise their ability to enjoy social occasions such as restaurant meals or family celebrations.[38] Practical advice from the perspective of other cancer patients, clear communication among family members, and self-help groups are often the best way forward.

Social roles are complex and multiple for most people. Many people with advanced cancer will occupy at least some of the following roles: partner, parent, worker, and friend. The performance of these roles and the satisfaction derived from them often determines perceptions of self. Managing role change in advanced cancer is threatening to self-esteem because people may have invested heavily in the performance of these roles. For example, employment provides many opportunities such as financial security, access to health insurance benefits, opportunities for fulfilling interactions, and social relationships with work-based colleagues, social status and power, enhanced self-esteem through knowledge and skill acquisition. Of course, not all work-related experiences are so life enhancing and some people relish the opportunity to quit certain working environments to redirect their energies in more fulfilling ways. A diagnosis of cancer and subsequent survival may precipitate a reappraisal of life goals.

Evidence from two ethnographic studies helps to illuminate the processes facing cancer patients living with advanced disease. Ethnography is a method of investigation in which the researcher develops a close relationship with people in their own context to gain access to understandings of their social world and culture.[39] An ethnographic study followed the experiences of a group of patients with advanced small-cell lung cancer from diagnosis to death in a cancer centre in The Netherlands.[40] The author describes in rich detail the experiences of patients, their spouses and families throughout their illness. She spent a great deal of time in the clinics listening to the doctors and nurses and sharing the experiences of the patients and their families as they underwent diagnosis, initial treatment, recurrence and through to their final days and deaths. We also learn about medical and nursing staff not as stereotypical consultant oncologists, junior doctors and ward nurses but as complex individuals who vary both between each other and also between their handling of each patient. The study addressed the questions about why and how patients remain so optimistic throughout their illness when the outcome is known (by medical staff) to be almost invariably fatal.

This research offers an antidote to simplistic communication research in cancer care which focuses solely on “the bad news” interview as though it were a single event. It demonstrates the complex interactions between patients, families, medical and nursing professionals in constructing what is “known,” and when and how it is “known.” The researcher argues that both patients and their doctors collude in minimizing the significance of the disease in the early stages by concentrating their attention on short-term outcomes such as planning and starting treatment. In the author’s view, this serves to deflect attention away from the more unpleasant long-term outcome which will be the patient’s inevitable death. Patients and their families come to understand the implications of their disease through social comparison processes with other patients. Once again, this is rarely acknowledged in the communication literature, where health professionals are often portrayed as virtually the only sources of information. By comparison, in this research we are shown how patients hear about the recurrences and deaths of their peers, and how they both learn from, and distance themselves from, these events. The author describes how nurses are placed in the difficult position of having to “fish” for information about the level of awareness of patients because they are not party to the communication that has occurred between medical consultants and patients. The picture of fluctuating awareness is akin to that described as “conditional awareness.”[41] The research paints a complex picture of the tangled web of truth, half-truths, and deceptions which are often the pattern of communication that patients, families, and health care workers participate in creating. Research on interventions that can alter these communication patterns and their effects on well-being seem warranted.

In another ethnographic study of cancer patients attending a British Cancer Centre,[10] an account is given of the experience of patients attending for radiotherapy. The authors argue that patients learning about their role of being "a cancer patient" through social comparison with and information from other patients. While the diagnosis of cancer is conveyed by the medical staff, they only learn what that truly means in their interactions with other patients. The social status of "cancer patient" has implications for every aspect of their lives because of changed communication styles and assumptions by their families (e.g., expressions of distress and solicitations) and their work colleagues (e.g., out-pouring of sympathy or distancing tactics). While some of these changes are perceived as helpful and supportive, others constrain their options (e.g., such as not being considered for promotion at work). The authors argue that the pervasive changes that follow a cancer diagnosis and into the uncertain period of survival profoundly impact on the patients and their families as they negotiate their illness and survival trajectory or "calendar."

6.0. COPING

In the next section, attention will be directed toward how people cope with advanced cancer. I will argue that the research literature tends to focus on psychological morbidity rather than examining well-being and resilience. Much of the early research in psychosocial oncology explored the incidence of, and reasons for, psychopathology in cancer.[42] This is important because it highlighted for the first time that survival alone was not sufficient to ensure a reasonably good quality of life. For example, research in the 1970s and 1980s demonstrated that high levels of depression and anxiety were common sequelae for women with breast cancer and were not directly related to the type of surgery.[43] Current systematic reviews indicate that a sizable minority of patients will experience psychological morbidity, usually anxiety and/or depression in the immediate period following their cancer diagnosis. Other key transitions such as recurrence of cancer and transfer between curative and palliative treatment are also associated with raised levels of psychological distress.[44]

7.0. UNDERSTANDING PROCESSES OF LOSS AND CHANGE

Much of patients' and families' experience of living with advanced cancer can be understood as coming to terms with a series of losses. These losses may be related to many aspects of a person's life, for example, their functional ability such as to walk unaided, to talk, and to be continent. In some types of cancer, such as cerebral tumors or those with cerebral metastasis, intellectual function may be compromised or lost and emotional expression may be blunted or emotional control may be lost. Arguably advanced illness is associated with a cascade of losses for both the ill person and their family members. Moreover, with open communication about the probable outcome of disease and greater awareness of prognosis, people in these situations may start to anticipate a series of losses that they have yet to experience. This has been described as anticipatory grief[45] and can be experienced by both the person with cancer as they contemplate their demise and by family members who fear the death of their loved one but also have to face a continuing life without their presence. It has been argued that when life-threatening illness is very protracted, especially if the ill person loses the capacity to communicate and relate socially, family members may start to withdraw from the ill person before their death. Sudnow[18] described the phenomenon of social death where in certain cases, there was a loss of personhood and the dying person was treated as if they were already dead. An ethnographic study conducted in an in-patient hospice in England described the situation of patients who had severe and deteriorating cancer.[28] For example, one patient was living with what for her was an intolerable situation, a recto-vaginal fistula that produced uncontrollable leakage of faecal material. The odor was so bad that her husband and even the staff found it difficult to remain in her room. The patient herself requested sedation until death to make her unaware of her situation. Lawton argued that in this case social death was the preferred option of the patient and those around her.[28] Now there are many things that can be attempted that can improve the management of these stressors by directly altering the sources of stress such as alternative surgical appliances.

There are a number of competing theoretical accounts of loss, change and coping which are worthwhile reviewing briefly in the context of living with advanced cancer. While these theories are usually applied to the irrevocable loss of bereavement they are applicable to understanding other life transitions and losses.[46] These theories fall into three conceptual groups dependent upon their major emphasis: intrapsychic processing, transactional approaches, and social models of loss. Perhaps the most dominant influence on clinical practice are models derived from psychodynamic psychology and psychiatry. These emphasize intrapsychic processing especially the cognitive and emotional aspects of managing loss. These theories can be traced to the early ideas of Freud[47] and his notion of "grief work" and the proposal of sequential stages or phases in adaptation to loss. This was developed by the British psychiatrist John Bowlby[48–50] into an account to explain mother and infant attachment behaviors and the effects of separation on the infant. Similar ideas can be traced to the phase models of Parkes[51] which he developed to explain bereavement outcomes and to Kubler Ross[52] who described emotional transitions in people who were aware of their dying status. Parkes[51] argued that major changes, like bereavement, challenged the assumptive world and it was this disruption to taken-for-granted ways of managing everyday life that was difficult to cope with. It may also explain the profound impact that threats such as a cancer diagnosis have on psychological equilibrium. These ways of construing loss have been heavily critiqued over the years because they make assumptions that responding to loss can be conceptualized as a series of sequential stages, that focuses on emotional aspects of loss and largely ignores the social aspects (see Payne *et al.*[46] for a more detailed critique).

An alternative way of conceptualizing loss is derived from cognitive psychology especially the transactional model of stress and coping.[53] This model proposes that any event may be perceived as threatening by an individual, and it is the meaning of the event for each individual that determines its stressfulness. The authors suggested that each event was thought about (called cognitive appraisal) to estimate its degree of threat (primary appraisal) and to determine and mobilize resources to cope with it (secondary appraisal). Coping may focus on dealing with the threat directly or may emphasize the emotional response. These different ways to respond are called "problem focused" and "emotion focused" coping. Once again these processes of coping with loss are conceptualized within a largely individual framework of autonomous appraisals and coping responses and takes little account of the social context, availability of resources or social relationships in which they are situated.

Sociological perspectives on loss have emphasized the social meanings attributed by societies to different types of losses. Based on extensive research in North America, Klass *et al.*[54] have challenged notions that successful resolution of loss involves "moving on" and "letting go" which have been fundamental aspects of many loss therapies (e.g., Worden[55]). It is argued that for many people adapting to loss involved incorporating some aspect of their previous relationship with the deceased person into their current lives but in a way that was tolerable and was not distressing. Tony Walter[56] a sociologist working in the UK, developed a similar theory in relation to the loss of a deceased person. He suggested that the creation of a durable biography in the form of a narrative which describes both the person who has died and the part they play in others lives was a functional and therapeutic way to cope with loss. A recent review of research on the "continuing" versus "breaking" bonds controversy has failed to establish which is most adaptive.[57] Research investigating these different approaches to coping with loss would enlighten future management and even prevention of some of the negative aspects of this complex phenomenon.

This leads on to considering the more positive aspects of living with advanced cancer which have been under represented in the research literature. What allows some cancer patients to cope so well with survival? The individual difference literature acknowledges the role of personality attributes such as hardiness and resilience.[58] Yet there is still much that it not known about well-being which is likely to be more than merely the absence of psychopathology. In a theory of hope in situations involving pain, loss and suffering, hope was defined as a combination of a determination to achieve a desired goal or end point and a plan for getting there.[59] When pain, illness, disability or any loss occurs, previously valued goals may seem or may actually be unattainable. This can precipitate hopelessness, bring acceptance or promote determination. People who demonstrate flexibility and willingness to modify or change some of their original goals, are most likely to remain hopeful. Snyder[59] argues that resourceful people have a number of goals in different areas of their lives and show an ability to substitute goals that are achievable for those that become unattainable. Interventions that help cancer patients to reappraise their goals one-step-at-a-time when faced with overwhelming challenges are likely to be supportive. The positive aspects of living with advanced cancer may include reframing life goals, reappraising priorities and focusing on new or previously undervalued activities. This may relate to important relationships, employment or voluntary endeavors or creative ventures. There may be the sense of seeing the world afresh and a new with more intense valuing of things like the natural world or personal faith.

8.0. NARRATIVES OF ADVANCED CANCER

To gain a greater insight into these positive aspects, the following section will draw upon recent research which has explored narrative accounts written by health care professionals and patients about the experience of living with advanced cancer.[60] These accounts provide rich detail about how individuals experience their disease and the influence this has upon their lifestyle choices, preferences for health care and priorities. In comparison, health professional's accounts are marked by their biomedical framing of patient experiences and the social construction of the "good" patient and the "good death."[60] The role of the media (television, newspapers, and

Internet) are influential aspects of contemporary life through which judgements are made, understandings are formed, and social relationships that affect cancer are unfolded. The relationship between these public images and private experience will also be considered.

9.0. ACCOUNTS OF SURVIVORS WITH ADVANCED CANCER

In an extensive review of the literature on the narratives produced by patients,[60] a number of genres of writing were identified including books, newspaper articles, personal diaries and letters, and electronic "blogs" posted on the Internet. Some are highly polished "professional" accounts written by professionals such as journalists and were produced with the intention of publication, others are more ephemeral or private in nature. They share some features such as the possible therapeutic value of writing,[61] they wish to be an advocate for change usually as the result of unsatisfactory health care services or to be memorialized.

The review focused specifically on those who had an awareness of impending death which makes it relevant to this chapter. The authors concluded that the reasons for these narratives include "the need to make sense of traumatic events surrounding a diagnosis of potentially terminal disease, subsequent treatment, facing death as the illness progresses together with the encroaching disability and debility, as well as charting the changes in relationships with loved ones, oneself and one's body image. Narrators express the wish to restore everything back to normal, they describe the chaos associated with death and dying, and they explore the quest for meaning that may be found in the experience of serious illness and facing death. There is a clear need for creating and renewing different constructions of self through the illness narrative and to ensure a continuity of self after death."[62] An analysis of a professional writer's account of his oral cancer is presented in Textbox 2. This area could benefit from further exploration of the relationship between this form of communication and quality of life outcomes.

Textbox 2. A Narrative Analysis of a Personal Written Account of Experiences During Treatment for Oral Cancer

John Diamond, a British broadcaster and journalist, wrote an account of his experience of oral cancer in a series of articles in *The Times* newspaper over a period of 4 years, from diagnosis to 1 week before his death. His account provided a narrative of one man's experience of living with cancer. Through writing the articles in the form of a diary he attempted to find meaning in his experiences and according to his brother-in-law, the writing was his method of coping with illness. Crossley[63] a health psychologist, undertook a narrative analysis of his articles which she interpreted in the context of the notion of 'therapeutic emplotment'[34]. Del Vecchio Good *et al.*[34] have argued that oncologists and patients creatively manage time and the patients' experience of illness as part of 'a larger therapeutic story' (p. 855). This serves to highlight particular events and episodes which appear to maintain the possibility of hope. Crossley[63] examined Diamond's articles for evidence of his unfolding story. She categorised them into six sequential stages.

1. *Pre-cancer: touch wood*
   In the first article on 14th September 1996, he reported the possibility that his mouth swelling *might be* cancer but distanced his self.
2. *Learning to live in "therapeutic emplotment"*
   Over the next six months Diamond's articles were full of accounts of various medical and surgical treatments and their associated side effects. His language appeared to be optimistic, with an emphasis on the future expectation that following 6 weeks of daily radiotherapy, and surgery he would achieve full recovery. He was encouraged to live in the "immediacy of treatment" while the future holds the promise of a certainty of outcome (cure).

3. *In limbo: holding one's breath*
   Following treatment, he comes to realise that "the truth is . . . I still don't know whether I'm cured. Nor will I know for weeks, or months, or possibly years."
   This period is some times described as 'watchful waiting' and can be even more stressful than undergoing active medical treatment (Jones and Payne[11]).
4. *Recurrence: "therapeutic emplotment" continued*
   Ten months after what appeared to be the "end" of treatment, his cancer recurred. Diamond tried to be optimistic in the face of further radical head and neck surgery. He wrote "if the surgeons slash and burn in the right way then I have a reasonable chance of a cure."
5. *Through the mirror: the "unspoken narrative"*
   Following surgery there is evidence that Diamond starts to abandon his previous expectations of cure and gives up his "almost childish belief in the power of modern medicine." However, he consents to chemotherapy which he describes as "stale hell" and some 4 months later another swelling in his neck is confirmed as cancer recurrence.
6. *Endings or the end?*
   The final period of writing is characterized by a lethargy and resignation. Further recurrence and spread to his lungs are responded to by his agreement to a further three courses of chemotherapy but with no optimistic expectations. One week later, he dies in hospital.

This is a tale of one person's experience of oral cancer. As readers we know the outcome, but as Crossley points out in her analysis, Diamond did not. How he engaged with this uncertainty is powerfully revealed in the writing.

(published with permission from Payne *et al.*[4])

10.0. ACCOUNTS BY HEALTH CARE PROVIDERS, RELIGIOUS AND FAMILY SUPPORT

An extensive review of the English language literature written by health professionals engaged in caring for dying cancer patients identified that there has been a number of transitions over the last 30 years which recognized improvements in palliative care and greater awareness of the benefits of hospice programs.[60] There was also greater acknowledgment of the psychological needs of patients and an interest in providing care within the context of multiprofessional teams rather than merely from medical or nursing perspectives. As evidence for this trend, there have been emerging accounts written by social workers, physical and psychological therapists, chaplains, and complementary therapists since the 1990s. However, physicians remain the most productive and dominant "voice" in professional accounts and serve to the shape practice and policy in this area. Analysis of the content of the written accounts reveals that professionals identify a wide range of needs for people with advanced cancer and particularly in North America tend to emphasize patient autonomy, control, and choice. These writings also reveal a growing prioritization of psychological aspects of managing advanced cancer, with assumptions that open emotional expression is helpful but emotions should be "positive" and facilitate "acceptance"—drawing upon the popular ideas of Kubler Ross,[52] rather than emotional expressions of anger, disruption, and guilt. There are therefore interesting tensions been the professional discourses of patient autonomy and choice and clear expectations about the "right" ways to deal psychologically with cancer which may limit permitted options for patients.

11.0. FAMILY CAREGIVERS

Finally, living with advanced cancer impacts on social relationships; so this last section will discuss the implication for families and informal carers who are in close contact with cancer survivors with advanced disease. A number of reviews of the literature from Australia,[64] the UK,[65,66] and Canada[67] have consistently highlighted the problems and challenges faced by family caregivers. The following section offers a summary of the main factors identified. Until relatively recently there was little acknowledgment of the needs of family caregivers.[66] It is only recently that patients and caregivers in the UK have been invited to contribute directly to national debates on health and social care or become involved in the planning and delivery of services and contribute to the design and conduct of research in health care.[68,69] Even within these new "user involvement" policies, carers in palliative care tend to be regarded as proxies for patients who are too ill or otherwise unable to articulate their own views rather than as having a mandate to speak about their own concerns.

Lay people who take on unpaid caring roles in relation to a person facing the end of life are defined as carers or caregivers.[70] According to the General Household Survey conducted in 2000, there are approximately seven million carers in the UK.[71] Most provide care for those with chronic illness, disabilities, and for frail older people. It is difficult to estimate the number of those providing care for a person with advanced cancer, as much will depend upon the definition of cancer survivorship used and whether the remit extends to those who provide psychological and social support or merely physical caregiving. Evidence suggests that greater numbers of people in the UK population provide care at some point in their lives than 10 years ago. More women (3.9 million) than men (2.9 million) provide care; and the majority are middle aged (between 45 and 64 years) but increasingly older people over 65 years, are involved in caregiving to older parents or spouses.[71] In the context of cancer survivors with advanced disease, there is more likely to be within generational than intergenerational caregiving. Caregivers are usually family members but changing social patterns such as divorce, geographical mobility, increased longevity, and declining birth rates, may mean that for some people, friends, neighbors or employed care workers (e.g., for older people living in care homes) may provide more meaningful relationships than geographically distant kin.

Much of the early research on caregivers emphasized the domestic and personal care tasks which were performed, this lead to a picture of carers being physically burdened by the labor of caring which has been critiqued.[72] In addition to providing care for the ill person, caregivers often take on additional responsibilities in managing the home, family finances, childcare, and care of other dependents such as older relatives. Family caregivers are increasingly being relied upon to provide the majority of daily care, including the management of the physical, emotional, and psychological consequences of advanced disease but professional service providers often are unaware of the complexity and nature of the caring role assumed by families. In a study of caregivers of those with cancer in the UK,[73] 21% of caregivers were already providing care to sick family members, children and/or dependent older family members before the cancer diagnosis. Evidence from Australia[64] indicated that caregivers reported reduced opportunities to engage in social and recreational activities which decreased their own health and psychological well-being. This compounded problems related to caregiving such as stress, social isolation, exhaustion, physical injuries such as back pain and they had insufficient time and resources to attend to their own health care needs. However, it is important to acknowledge the rewarding aspects of caregiving which many family members report, including the enhanced and intimate relationship fostered during the caring experience, and the sense of personal satisfaction and social esteem from doing what they perceive as their duty and fulfilling a moral obligation.[72] Now that we have described many of the challenges it is time that research studies find ways to address these problems in order to improve emotional distress and interpersonal strain on all parties involved.

Depending upon the health care systems operating in different countries, family members may also face severe financial hardship in meeting medical bills and medication costs. The evidence suggests that caregivers in all countries experience additional costs for example in providing transport for hospital clinic visits and in purchasing home equipment, modifications, additional heating/air conditioning, and special foods. While facing additional family expenditure, caregivers are likely to experience difficulties in maintaining employment. They may be forced to reduce their employment hours or even give up work and rely on government assistance programs which may result in long-term consequences for their own financial security and pensions. A recent review of the research literature indicated little attention to effects of caregiving for those with advanced cancer on the employment and financial consequences of caregivers.[74] More research in this area is urgently required.

In many countries, assumptions about the availability and willingness of family caregivers to provide support and care lie at the heart of community health care policy. Over the last few years services to support family caregivers caring for those with advanced cancer in countries like Australia,[64] Canada,[67] and the UK,[65] have moved from the margins of health and social policy to occupy a more central role. The impact of family caregivers' policy changes in the UK[75] which has resulted in an emphasis on community care and the movement away from care delivered in institutions remains unclear. Notwithstanding such advances, a major review of the recent general caregiving literature[76] has identified several unresolved questions in relation to caregiver support, including:

- *When* is support best provided?
- *How* is support best provided?
- *What* are the intended aims of support?
- *Who* is the perceived beneficiary?

There remains relatively little evidence for the effectiveness of services.[65] For example, a review of the literature on palliative care respite services for those with advanced cancer failed to demonstrate strong evidence of its efficacy in supporting family members.[77] A probable cause of the problem lies in the fact that services are often inflexible and fail to provide sufficient care and support that caregivers see as being of high quality.[78] All too often the outcomes of services are not those that caregivers see as important,[78] and there is a general failure to engage fully with caregivers as co-experts in care delivery.[79] Consequently, services are often viewed as obstructing or inhibiting caregivers' goals, rather than facilitating them.[79]

Research has long been recognized as an important way to develop and improve clinical services to cancer survivors with advanced disease. However, there is also evidence to highlight the ethical, methodological, and practical problems in conducting research with people who have advanced disease.[80] Textbox 3 lists the main topics that could benefit from further research. A range of methodological approaches is desirable depending upon the research questions asked. In-depth qualitative studies may be helpful to illuminate the understandings and experiences of cancer survivors and their families, while clinical trials are also needed to test the efficacy and cost-effectiveness of interventions. Mixed methods approaches such as case study methodology can have advantages in real world situations where it is necessary to capture the process of change as well as measuring final outcomes. These challenges in research are better met by strong collaborations between clinicians and scientists to ensure both methodological rigor and clinical applicability.

Text box 3. Topics for Further Research on Cancer Survivors with Advanced Disease

- Transitions in identity as a cancer survivor
- Understandings of "health" while living with advanced cancer
- Impact of continued medical surveillance and perceptions on discharge from medical care
- Interventions to manage permanent and temporary physical symptoms
- Interventions to manage effects of changes in appearance, both temporary changes and permanent ones
- Interventions to support transitions in social roles such as giving up paid employment.
- Interventions to enhance communication between health care workers and cancer survivors
- Explorations of the use of new technologies to provide accessible communication and information, when required.
- Interventions that explore the efficacy of different communication styles and patterns
- Investigation of cancer survivor's preferences for place of care
- Investigation of the impact of multiple losses due to advancing disease
- Development of quality of life measurement tools that take account advancing disease
- Interventions to support families live with the uncertainty of cancer survival or recurrence.

12.0. CONCLUSIONS

The evidence that has emerged during the production of this chapter shows that people with advanced cancer can be construed as "survivors." The general palliative care literature tends to "frame" these same people as "dying" but in many ways that is incorrect except in the final stages of physical deterioration. An alternative is to view these people and their family caregivers as "cancer survivors." Increasingly cancer patients will live for longer periods with the knowledge of their advanced disease and the threat of recurrence. These represent both physical and psychological challenges for individuals. This chapter has reviewed the consequences of physical impairment, changes to appearance, functional limitations and psychological sequelae. There has been a tendency in my view to seek to identify pathology instead of recognizing the profound adaptations required and the resilience of many cancer survivors. The chapter has also reviewed the social impact for patients and family members.

Many patients and family are fortunate to receive high quality, comprehensive and well-coordinated multidisciplinary cancer care. The development of specialist palliative care services and hospice programs throughout the world have made dramatic improvements to the lives of those who are able to access these services but in most countries these people remain the minority. Calls to extend the principles of palliative care to all cancer patients who may benefit have been made.[81] This requires a radical shift in the organization, management and funding of these services so they become part of standard oncology provision. They also need to be made available in flexible formats in response to differing social circumstances and preferences about place of care. These new ways of extending the remit of supportive palliative care rather than merely focusing on terminal care have been proposed to be health enhancing.[82] They require new ways of thinking from government agencies, major cancer charities and of course, support from the communities in which they are embedded. We need to look to exciting new models of community-based nonprofessional palliative care emerging from less well-resourced countries such as India.[83]

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Part V

International Perspective

Chapter 25

Global Considerations

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1.0. INTRODUCTION

On a global basis, 10 million individuals are annually diagnosed with cancer. It is estimated that by the year 2020, 15 million new cancer cases will be diagnosed.[1] The most commonly diagnosed cancers internationally include lung cancer (1.35 million), breast (1.15 million), and colorectal (1 million).[2] The International Agency for Research on Cancer (IARC) reported that in the year 2002 there were 24.6 million persons globally surviving with cancer.[3] The most prevalent form of cancer is breast cancer with 4.4 million survivors.[2] While cancer is the second most common cause of death in developed countries, this is also a growing trend in developing countries.[4] Cancer has become a significant health burden internationally with survivorship not always being attainable for a variety of socioeconomic, cultural, and environmental reasons that will be explored throughout this chapter.

2.0. CANCER SURVIVORSHIP WORLDWIDE

Just what is the descriptive epidemiology of cancer survivorship in the world today? While there is no single source for this information yet I will attempt to provide a worldwide perspective. The main source of international cancer statistics is the IARC. In 1975, this agency began estimating the burden of incident cancer cases for 12 common forms of cancer throughout the 24 different countries where the United Nations collected data.[3] These forms of cancer included mouth/pharynx, esophagus, stomach, colon/rectum, liver, bronchus/lung, breast, cervix, prostate, bladder, lymphatic tissue, and leukemia. Since the 1960s, individual countries had collected registries on their populations, but until recently this was done without coordination or collaboration among or between the nations. In 1989, the EUROCARE project was established by the European Community under Health Service Research to determine and assess international variation in cancer survivorship. The EUROCARE-1 reported on the survival of 800,000 cancer patients who were diagnosed during 1978–1985 and followed up to the end of 1990. These individuals were in 30 population-based cancer registries from12 European countries that included Denmark, England, Estonia, Finland, France, Germany, Italy, The Netherlands, Poland, Scotland, Spain, and Switzerland. This study represented the first population-based collection and analysis of survival data on cancer patients using a common methodology.[5] This endeavor was a significant step forward in addressing and quantifying cancer survivorship globally.

The EUROCARE-2 study followed individuals from 1985–1989 through 1994,[5] building upon the EUROCARE-1 data to look at trends in survivorship and to examine what the trends meant in both time and geographic region. Results from EUROCARE-3 were reported in 2003. This phase of the study examined 1,815,584 adults and children from 22 countries with 67 participating registries from the period 1990–1994 and followed up to the end of 1999.[6] The goal of this phase was to better understand the survival differences seen overtime and the various populations to examine how earlier diagnosis, differences in types and benefits of treatments, and the interaction of these two impact survival rates.[3] Results of EUROCARE-3 are presented in Figure 1 showing that the average survival rates range from less than 4% for those with pancreatic cancer to a high of 94% for those with lip cancer. Survival rates in this study, for all tumors considered together, were found to be higher for women than men, and higher in the younger versus the older patients.[2] Figure 1 depicts this pattern, showing in 30 of the 35 cancers that the cancer rate was higher in women than men for cancers that occur in both sexes.[6]

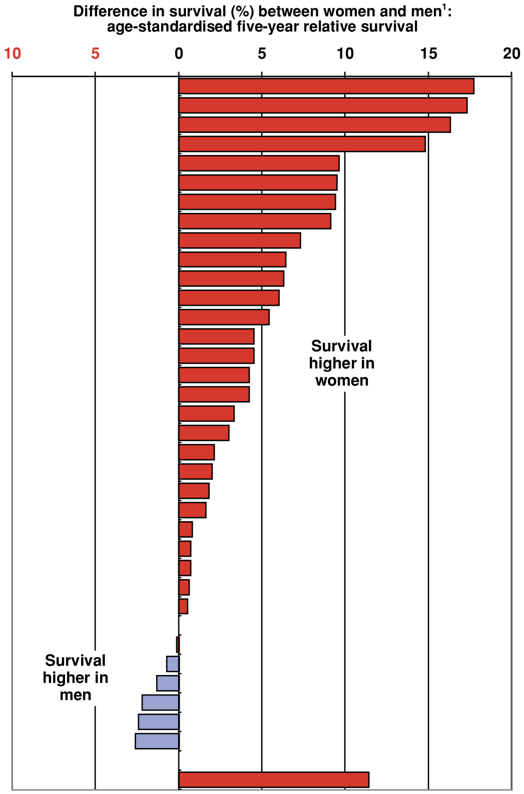
Broadening the EUROCARE focus by including other counties, the IARC obtains its data from cancer registries maintained by individual countries, combining them into a single dataset entitled GLOBOCAN. GLOBOCAN is a combination of EUROCARE, the Surveillance, Epidemiology, and End Results (SEER) program of the United States, and the Cancer Survival in Developing Countries project conducted by IARC.[3,7] The focus of GLOBOCAN is on measuring incidence, mortality, and prevalence of cancer on a worldwide basis.

Most of the European nations maintain cancer registries, but not all contribute to the EUROCARE project. Other nations maintain and report on their own registries, such as the Australian health care system which is able to report that the 5-year survival rate for individuals diagnosed with cancer at nearly 50%,[8] with about 270,000 Australians living with cancer,[9]

Some countries have not been able to establish registries; most developing nations find creating and maintaining a registry difficult because medical records and other vital information is not uniformly or consistently recorded, and population denominators are not always known. For example, researchers at the Institute of Pasteur in Madagascar did attempt to review the epidemiology of cancer in Madagascar, but found their review not to be representative because of an extremely low rate of health care coverage across the nation, particularly in the rural areas, and that some types of cancers are hard to quantify as there is not diagnostic equipment available.[10]

Quantifying the number of survivors is a difficult task, as discussed above, because such data are not readily and comprehensively collected on an international basis. However, it seems to be agreed upon in the scientific community that *survival* means the individual is at least 5 years post-cancer treatment, and in some communities, the individual is considered *cured.*[7] Many researchers have begun to reconceptualize cancer as a chronic illness as more people are living longer after treatment,[11] yet as the chapters in this book indicate there is no universal agreement on the definition of cancer survivor, with some considering any time since

MALIGNANCY	Women No. of patients	Women Five-year survival	Men No. of patients	Men Five-year survival
Salivary glands	1,612	**68.7**	1,926	**51.0**
Tongue	2,302	**52.2**	5,555	**34.9**
Oral cavity	3,431	**56.9**	7,315	**40.6**
Oropharynx	1,170	**43.5**	5,015	**28.7**
Thyroid	9,953	**81.4**	3,203	**71.8**
Melanoma of skin	26,793	**84.3**	20,625	**74.8**
Nasopharynx	573	**49.3**	1,299	**39.9**
Hypopharynx	868	**32.3**	4,029	**23.2**
Choroid (melanoma)	967	**72.3**	1,099	**65.0**
Chronic myeloid leukaemia	2,687	**36.9**	3,391	**30.5**
Hodgkin's disease	4,658	**81.5**	6,179	**75.2**
Non-Hodgkin lymphoma	27,068	**53.7**	30,702	**47.7**
Stomach	34,871	**25.4**	55,254	**20.0**
Rectum	40,463	**49.6**	52,504	**45.1**
Multiple myeloma	11,501	**33.0**	11,951	**28.5**
Nasal cavities	1,330	**48.0**	2,046	**43.8**
Chronic lymphatic leukaemia	6,411	**66.4**	8,973	**62.2**
Bone	1,241	**56.3**	1,515	**53.0**
Kidney	18,082	**57.2**	28,536	**54.2**
Brain	11,976	**18.5**	15,611	**16.4**
Oesophagus	11,491	**10.5**	21,702	**8.5**
Colon	78,258	**51.0**	72,234	**49.2**
Small intestine	2,039	**39.2**	2,214	**37.6**
Pancreas	25,004	**4.6**	24,070	**3.8**
Acute myeloid leukaemia	5,555	**13.4**	6,220	**12.7**
Pleura	1,374	**5.5**	5,564	**4.8**
Breast	256,464	**76.1**	1,809	**75.5**
Liver	7,368	**6.7**	12,747	**6.2**
Soft tissues	4,612	**54.2**	5,675	**54.2**
Lung	68,463	**9.6**	183,514	**9.7**
Biliary tract	12,164	**11.6**	6,591	**12.3**
Larynx	2,590	**59.4**	19,669	**60.7**
Lip	1,231	**90.3**	4,964	**92.5**
Bladder	25,558	**67.1**	78,514	**69.5**
Acute lymphatic leukaemia	1,068	**21.6**	1,405	**24.2**
Total	*711,196*		*713,620*	
All malignant neoplasms[2]	**878,319**	**51.2**	**911,574**	**39.8**



[1] Absolute difference—e.g. for kidney, 57.2% – 54.2% = 3.0% (see text)

[2] Excluding cancers that only arise in one sex

Figure 1. *Source*: Coleman *et al.*[6]

diagnosis as survival time,[12] while others have used this 5-year mark as the defining point because many physicians consider the risk of recurrent cancer being greatly reduced by the fifth year.[13] GLOBOCAN uses the 5-year definition for their prevalence estimates; therefore, they are able to estimate a level of survivorship globally defining prevalent cases as those "alive with cancer" meaning that the individual is either receiving treatment or possibly being followed up with ongoing medical care. Individuals may have been diagnosed with cancer prior to the establishment of a registry, therefore, longer-term survivors may have been undercounted,[14] or loss to follow-up over represent the numbers.

None-the-less, maintaining some form of a cancer registry is critical to the World Health Organization's (WHO) mission to promote early detection and treatment to try to control the spread of cancer, and in turn, enhancing chances of survival. The survival statistics collected by registries, including incidence and mortality, are a way of monitoring effectiveness of the WHO's mission on population levels.[15] Table 1 presents the comparison of survival rates by country using SEER registries and the EUROCARE3 registries. The numbers in the table depict estimates of survival based on the ratio of age-adjusted mortality and incidence of 11 significant cancers in eight different countries, with the world divided into two areas: developed countries and developing countries. The table reveals that survivorship is more likely in the developed countries over the developing countries, with Eastern Europe being an exception where those rates are lower than South America for many types of cancer. The nations of Sub-Saharan Africa fair the worst overall. However, data related to cancer survivorship in Africa are scant, but because of the tremendous effort that has been placed on population-based cancer registries in this continent, more information on survivorship will be elucidated in the coming years. The principal factors contributing to the disease pattern seen in this table reflects countries where there are increasing numbers of the elderly (a population in which cancer is more prevalent), the increase in medical science's ability to manage cancer, and the increase in some types of cancer, particularly, lung cancer from tobacco use. Therefore, some nations will see an increase in survivors where others will not.

Distinct geographical variations in the incidence patterns by type of cancer are influenced by risk factors present in the different environments. Furthermore, it has been noted that the affluence of a country affects the overall cancer survival rates, with greater affluence resulting in higher survival rates, depending on how the reliability and accessibility of the screening, diagnostic, and treatment systems.[2]

The IARC has found that individuals are more likely to survive following cancers of the head and neck, large bowel, breast, melanoma, cervix, ovary, and urinary bladder. Early detection is the greatest factor to influence survival in those cancers.[15] The differences between developing and the developed countries with respect to survival is that the greatest disparities are found in cancers where multiple modalities are needed for care, including access to a combination of crucial medications, chemotherapy, radiation treatment, and the trained personnel for care delivery. These cancers include those of the testis, leukemia, and lymphoma.[15]

Overall differences in survival rates have been attributed to variables such as stage of the cancer diagnosis, the availability and quality of health care services, the type of cancer treatment received, and the follow-up care received, if any.[15] Additionally, there are individual level variables that also contribute to the variation in survival rate including socioeconomic status, attitudes and beliefs about treatment, and adherence to the treatment recommendations.[15] Similar work at the population level has not been undertaken.

Table 1. Estimated Age-Adjusted Survival (%) from 11 Cancer Types, by Country/Area

	Developed areas					Developing areas				
	United States	Eastern Europe	Western Europe	Japan	All developed areas	South America	India	Thailand	Sub-Saharan Africa	All developing areas
Esophagus (male)	14	6	18	25	15	7	13	13	4	17
Esophagus (female)	8	2	14	15	8	5	14	10	5	16
Stomach (male)	44	15	30	54	35	25	14	12	7	21
Stomach (female)	33	16	24	51	31	24	14	14	5	20
Colon/rectum (male)	66	35	56	65	56	50	28	37	13	39
Colon/rectum (female)	65	36	53	58	54	50	31	37	14	39
Liver (male)	20	≈ 0	≈ 0	9	6	≈ 0	4	3	2	5
Liver (female)	0	≈ 0	≈ 0	12	0	≈ 0	9	3	1	3
Lung (male)	21	9	9	15	13	8	12	5	4	12
Lung(female)	26	10	14	22	20	1	11	5	5	12
Kaposi sarcoma (male)										
Kaposi sarcoma (female)										
Breast	81	58	74	75	73	67	46	62	32	57
Cervix uteri	70	51	66	65	61	55	42	58	21	41
Corpus uteri	89	69	83	79	82	70	59	67	61	67
Prostate	87	44	72	55	76	62	35	36	21	45
Leukemia (male)	43	29	43	25	40	24	19	15	14	19
Leukemia (female)	45	29	45	29	39	24	19	15	17	19

Source: Parkin, *et al.*[3]

3.0. INTERNATIONAL HEALTH SYSTEMS

Much of what contributes to cancer survivorship depends upon the health care system and the economic environment within which the individual must interact.[16] Health care systems vary tremendously among nations, as does the economic infrastructure of the nations themselves.[16]

In Europe, most countries do not attach health insurance to employment; therefore, losing a job does not mean the individual loses their health insurance. The removal of the economic threat of losing health insurance for ongoing care needs, and the provision of quality care for both the rich and the poor, at minimal or no cost, is a goal of the health care systems in the United Kingdom, Germany, France, Denmark, and Norway.[14] Conversely, nations without such economic resources and organized health care are in weaker positions to address cancer survivorship and all the medical and psychosocial issues it entails.[14]

On the other hand, India is trying to reduce the burden of those with cancer by offering a cancer insurance plan[17]; this plan covers the cost of treatment and ongoing care, but the individual must have purchased the plan prior to diagnosis. Also, all treatment needs to take place in India and must be conventional-based medicine, not complementary in nature. The insurance plan that may be purchased varies in the amount of coverage one wishes to establish for one's self. Table 2 below outlines the coverage under this plan based on the desired level of coverage. If the person is subsequently diagnosed with cancer, the individual is allowed reimbursement of expenses for treatment, hospitalization, and testing related to his or her condition, up to the insured amount. An individual is also able to take a one-time lump sum payment. Once the individual has cancer, he or she is allowed a renewal annual benefit as long as the policy's annual premium is paid; India's Cancer Patients and Aid Association, a charitable nongovernmental organization (NGO), has intervened to ensure this limit is renewed to handle ongoing needs, as well as helping to pay premiums to prohibit any lapse in policy coverage.[17]

In sum, a country's health system's organization and availability of health professionals with adequate equipment is fundamental to ongoing care however actual comparisons of these factors and actual survivorship among various cancers and across nations and systems of care require careful investigation.

3.1. Developed Countries

Many of the European health care systems engaged in vast reorganization in the end of the last century. For example, in the Czech Republic, Estonia, Poland, Slovakia,

Table 2. 15-Year Comprehensive Scheme (Effective 21st August, 2003)

Category	Sum insured (Rupees/Approx US $)[a]	One time lumpsum payment (Rupees/Approx US $)[a]
I	30,000 / $ 681	2,400/ $55
II	50,000 / $1136	3,000/ $68
III	100,000 / $2723	4,700/ $107
IV	150,000 / $3409	6,300/ $143
V	200,000 /$4545	8,000/ $182

[a] Amounts are converted to 2006 US dollars.
Source: Cancer Patients Aid Association.[17]

and Slovenia, the focal point for change was on increasing the participation of the private sector in health care. In the northern European countries including Denmark, Iceland, Finland, and Sweden, the reorganization sought to reaffirm the already established public sector systems. Whereas in other parts of the United Kingdom and in some southern European nations, including England, Scotland, Wales, Malta, and Italy, the public role has actually been diminished while still keeping health care in the public sector.[16] The remainder of the European health care systems by and large retained their previous structures that used a mix of health insurance-based systems with a private sector insurance component.

Over the years and despite all the change in the mix of coverage for health care services provided in the developed countries has broadened efforts to detect and diagnose cancer more readily, and include some form of treatment program. These efforts continue to evolve as research progresses. However, the linkage to programs focused on survivorship has not yet been realized for many countries. Most countries have focused on defining the magnitude of the problem through the development of registries, as discussed above, so programs can be developed to improve early recognition and treatment and only subsequently to support the health care needs of the survivor.

However, the impact of health care reorganization on cancer care has been a catalyst to develop cancer survivorship programs extending previously established cancer detection and treatment programs. For example, in England the National Health Service Cancer Plan in 2000 outlined the first comprehensive cancer care plan for that nation.[18] Currently, England has set forth a main objective that by the year 2010, 5-year cancer survival rates will compare with the best cancer care programs in Europe. The plan created cancer care networks that brought together health service commissioners (health authorities, primary care groups and trusts) and providers (primary and community care and hospitals), the volunteer sector, and local authorities to ensure that all cancer patients would have equal access to the best available specialty care services. They serve the ongoing needs of survivors through Cancerlink, a national charity-based program of Macmillan Cancer Relief. Cancerlink hosts a website, support groups, and free call in support line. Whereas this is a well-supported program, studies need to be undertaken to examine the effectiveness of Cancerlink.

3.2. Developing Countries

It has been found that the Western medical model's predominant use of professional medical personnel was not effective in these developing societies because of the rural nature of the countries, their high levels of poverty, and the general decline of the world economy. For example, in Africa, there are less than 100 radiotherapy machines available, which are hardly enough to meet the estimated need. Generally, it is the high cost of equipment, poor infrastructure, and the inadequate numbers of trained personnel are seen as the cause for shortage of the radiotherapy machines across the continent.[19] Thus, even though many Third World nations do have some of the highly technical procedures available to them to treat cancer, the poor and rural nations are unable to utilize those procedures causing higher rates of death from cancer despite the significant efforts by the WHO to increase screening and early diagnosis of cancer, but efforts are underway to increase access to necessary equipment and personnel. Parts of India are increasing their rates of diagnosing cancer to eventually begin earlier treatment. The International Atomic Energy Agency has facilitated the establishment of radiotherapy facilities in Mongolia, Ethiopia, Namibia, and Ghana, as well as providing ongoing aid to nearly 80 other developing states to enhance their radiotherapy facilities and staff training.[20] With the increased availability of equipment and resources, cancer survivorship will become more of a concern in these countries and will need to be addressed in the future. It is anticipated that the need for services for cancer survivors in these countries will increase considerably as survivorship begins to improve.

The WHO is working to improve the approach to cancer internationally, and to particularly support the developing nations, specifically working with the NGO's in each nation as is possible,[21] refocusing on cancer as a chronic disease, shifting from acute and episodic care management to manage longer-term chronic illness. Communicable diseases continue to be a relevant concern in many nations and new infectious diseases emerge on a regular basis,[22] however a primary care-based system in these countries that cannot manage chronic problems such as cancer and diabetes will not remain viable.[23] The WHO is also seeking to reduce the amount of fragmentation in care delivery, particularly as the care of the chronically ill requires coordination and integration among settings, providers, and across time. Reducing this fragmentation may improve health, decrease waste and inefficiency, and be less trying on patients to deal with systems. Additionally, the WHO understands the value of the patient and the family working together in the care of the chronically ill; the WHO hopes to shift the patient from a role of passivity to one that promotes self-health with the support of clinicians who educate and broaden their care to beyond the clinics and into communities.[4]

The most significant new model being used by the WHO is a framework built upon the work of many in self-management,[24,25] and an approach to modify health behavior within primary care.[26] This model was designed to organize the care provided for those with chronic conditions to enhance the outcomes of that care including: the community, the health system, self-management support, delivery system design, decision support, and clinical information systems. The model applied to chronic illnesses in the primary care environment is called the Innovative Care for Chronic Conditions (ICCC) Framework.[27] This model has been broadened to include patients and their families as well as those in their care environments such as their communities and their health care entities.

The WHO is also working with developing communities to realize their roles in working with those with chronic illnesses to enhance the level of integration of care at all levels. However, while many developed countries continue to struggle with resources allocated to many competing illnesses the WHO recognizes that developing countries are particularly in the position of "double jeopardy" as they are continuously challenged with two competing priorities. They must continue to deal with the infectious diseases, malnutrition, and the maternal/perinatal issues that have existed over many years, and now they must also cope with the increased prevalence of chronic conditions such as cancer, depression, and heart disease.[27]

4.0. INTERNATIONAL PERCEPTIONS OF SURVIVORSHIP

The face of international health has changed over the last century from where acute illness and death occurred at a much earlier age to an illness burden that reflects chronic illnesses and diseases like cancer. Chronic illnesses require longer-term treatment in an environment that can support continuity of care. Additionally, the amount, type, and focus of that care not only varies by economic conditions, but care is also guided by the sociocultural characteristics and history.

Social attitudes play a strong role in all cultures. For example, Europeans unlike some Americans wouldn't wear a ribbon or button indicating their status as a cancer survivor, nor would public figures readily share their struggle openly.[14] In many situations the diagnosis may be difficult to hide, so a ribbon does not need to be worn to symbolize survivorship because a much more explicit symbol presents itself, for example, in the form of lack of availability of skin color-matched prosthetics for use by non-white cancer survivors[28] or the presence of sudden functional losses. However, the stigma of cancer has been shifting with increased media attention and educational effort.[28] In their efforts to ease the negative perceptions of cancer, cultures may respond with an opposite response and expect that once treatment is over, the individual is "cured" and should just return to their usual life activities. This response stems from the belief of some cultures, that if you have cancer, you are expected to die, so if you do not die, then you must be able to get back into your "usual" life; similarly, many in Portugal, for example, consider a cancer diagnosis a death sentence.[14]

5.0. INTERNATIONAL/CULTURAL PERSPECTIVES ON QUALITY OF LIFE

With the likelihood of cancer survivorship increasing, support and ongoing care for the survivors moves to the focus of care; however, survival and living with the deficits that the cancer and its treatment may have caused is colored by the culture within the individual survivor resides. Notably, until recently in Japan, physicians would not share a cancer diagnosis with a patient, feeling that such knowledge would have a dramatic psychological effect on the individual, thus harming their quality of life.[29]

What is meaningful survivorship in one culture may be very different in another, often defined as the cultural consensus on what quality of life means. For example, Chaturvedi found in a sample of Indian cancer patients, family members, and their caregivers the 10 most important factors related to quality of life.[30] In this culture, she found that the level of individual functioning was not nearly as meaningful to them as was having "peace of mind," "spiritual satisfaction," "satisfaction with religious acts," and "happiness with family." These results contrast the values that most North Americans and Europeans have regarding the importance of the independence of the individual.

Similarly, Juarez *et al.*[31] spoke with cancer patients who were of Mexican ancestry. Reporting on what quality of life meant to them, these patients equated quality of life with being happy, remaining in an active lifestyle, and interacting with family. The four domains of quality of life, physical, psychological, social, and spiritual, were all influenced by the role of the family and the Hispanic's faith in God. Pain was noted by many Hispanics as needing to be endured because it was a component of life that helps one reach heaven. Additionally, frequently the use of the word "cancer" is not even spoken, with many family members wanting to keep this from the patient believing they may die sooner if they knew. This then has implications for the type of support family members offer one another. Findings of this study identified the importance of considering the Hispanic culture in the care of survivors.

A more recent study conducted in Hong Kong to better understand the adaptation process of Chinese gynecological cancer survivors also illustrates the role of culture in cancer survivorship. It was reported that the Chinese women felt that the cause of these types of cancers, similar to other "sexual disorders," was a result of an imbalance of the Yin and Yang elements due to excessive sexual activity that has, in turn, weakened the female body.[32] Other factors, such as education level,the patriarchal family structure, and the submissive role of women within the culture were also thought to influence beliefs about cancer.[33] These factors were found in another study of 62 long-term gynecological cancer survivors where it was demonstrated that many of the women felt guilty for not being able to meet their husband's sexual needs and felt the disharmony in their sex lives.[34] The Chinese women in this study defined quality of life as having mobility, accepting one's outlook, social support, and being able to eat. This focus on practical functional matters follows from the tendency that the breast in Asian cultures does not hold the same meaning on a sexual or body image level as it does in Western society.[35]

Some perceptions and cultural beliefs find the Chinese population to perceive that cancer is infectious, and related to certain excessive behaviors. In studies related to gynecological cancer, women believed that the cancer will recur if they have sex after treatment or that sex will cause the cancer to progress.[32,36] On the other hand,most of time the traditional healers or folk practitioners are able to spend more time with their patients attending to personal and social issues of helping the individual, for example, regain the balance in life, the balance that Chinese healers believe becomes disrupted and seen as producing the tumor (Traditional Chinese medicine does not use the concept of cancer, but it does use the concept of tumor.)[37] This time spent with the patient addressing this imbalance may culturally be more of what a cancer survivor may require.[38] For example, folk healers are typically closer in social class to the patients they are working with, and the emphasis on explaining the medical problem more closely aligns with the patient's understanding of how disease and illness occurs (i.e, the imbalance of energy).[38] In western nations various behaviors are ascribed to problems in health as well such as overeating, inactivity, smoking talk about need to look at attitudes and health across cultures and how to maximize health behaviors as per cross cultural risk factors for chronic illnesses or problems that occur secondary to cancer in cancer survivorship.

5.1. Developing Countries

It is well known the developing countries lag behind the industrialized nations on many fronts related to environmental health and health care,[22] affecting their views on what cancer survivorship means. In most Third World countries, the focus of health care is on a basic, primary prevention and primary care level. For example, Africa views cancer as an emerging public health issue, partnering with the HIV/AIDS outreach programs to address the control of cancer, especially ones of growing incidence related to HIV-associated malignancies and cancers caused by exposures to carcinogens in the African environment.

The WHO's Millennium Development Goals included aspects of eradicating poverty and hunger, enhancing maternal health,reducing childhood mortality, and combating HIV/AIDS, malaria,and tuberculosis.[39] These goals also included plans to increase sanitation levels, education rates, and the empowerment of women. Given the priorities and complexities of achieving the preceding goals, the role of cancer prevention, diagnosis, and treatment remains secondary. However, as discussed, these countries are now being included in world cancer registries to gain a better understanding of the magnitude cancer within their countries.

6.0. CANCER SURVIVOR PROGRAMS IN OTHER COUNTRIES

Following the establishment of registries to help quantify the actual number of their populations identified with cancer, many countries have begun to develop comprehensive cancer care centers (e.g., Sweden, France, Germany), however, as previously mentioned most continue to be focused on the diagnosis and treatment of the condition, with some just beginning to broaden their focus to include cancer survivors in their care networks.

As noted earlier, the health care systems in Europe, Canada, and Australia have been reevaluating their delivery systems to improve national health programs. The most significant strides in the area of cancer survivorship programs have come from the United Kingdom, basing their restructuring on clinical audits.[13] This reprogramming has shown a shift from a more traditional unidiscipline delivery system of care (e.g., Medicine, Surgery, or Obstetrics, and Gynecology) to a disease- and organ-based multidisciplinary delivery system. Most notably, has been the development and implementation of The Expert Patient Program. This program has also been used in Australia, Europe, and the US.

The Expert Patient Program, is based on the Chronic Disease Self-Management Program (CDSMP) developed and researched over the past 20 years by researchers under the direction of Dr. Kate Lorig at the Patient Education Research Center at Stanford University, and also on the work of Dr. Edward Wagner in the primary care setting. The Expert Patient Program trains chronic illness survivors of all types to develop and enhance skills to self-advocate and to manage their care better on a daily basis.[40] Beyond the individual patient goals, the program focuses on the broader system of health care and works to improve quality of care, reduce geographic barriers that negatively influence outcomes of care, and to enhance the overall coordination of the care. Whereas this program is not specifically focused on cancer care, it does have applicability to that population.

Another interesting national program in England is called Cancerbackup (British Association of Cancer United Patients—and their families and friends). The description of the program can be found at http://www.Cancerbackup.org.uk. This site is Europe's leading cancer information service, with several thousand pages of current cancer information, practical advice and support for cancer patients, their families and caregivers. Cancerbackup is interested in continually refining its program to ensure it is meeting the needs for whom the site is intended. In general, Cancerbackup has several mechanisms evaluate its programming. It seeks to identify specific groups of individuals (e.g., men, minorities, full-time workers) who do or do not use the service, and the extent to which they use the services. They are interested in finding ways to more fully develop their existing serivces. They are also interested in assessing the effectiveness of various strategies to enhance the number of contacts they receive from the different groups, evaluating how the media effects the numbers of contacts, and making their data available to professionals and the general public to increase awareness of their services.

Table 3 highlights some of their most recent research articles and their findings supporting their defined areas of cancerbackup's research mission. All studies indicate topics for further research in the areas they explored. Furthermore, the organization is interested in having researchers analyze their data to explore the types of information sought by individuals affected by cancer. The organization is sponsoring a proposal competition for interested researchers. They are encouraging the

Table 3. Overview of Outcomes Research Completed by Cancerbackup

Article	Findings
Hardyman, R., Hardy, P., Brodie, J., and Stephens, R. 2005. It's good to talk: Comparison of a telephone helpline and website for cancer information. *Patient Education and Counseling* 57, 3: 315–320.	This study explored the types of information people sought using telephone helplines and the Internet. The results of the study illuminated the types of health information people seek between the two sources and how the sources could complement each other to benefit survivors.
Boudioni, M., Mossman, J., Boulton, M., and Hardy, P. 2004. Differences in enquiries to CancerBACUP information service by living arrangements. *European Journal of Cancer Care* 13, 1: 6–10.	The study's goal was to address whether an individual was more likely to be able to live alone if they had access to and independent cancer information service. The study was not able to confirm that individuals with cancer were more likely to live alone with access to the information service, but was able to explore some of the differences in use of the service by these individuals.
Hardyman, R., and Leydon, G.L. 2003. Letter: Media influence behaviour. *British Medical Journal* 326: 498.	These researchers examined the impact of a news media (television and related tabloid newspaper) article the death of a fictional television character of cervical cancer. They examined the number of calls to CancerBACKUP's helpline in the time, finding peaks in the numbers of calls that they received at the breaking of the news of the cancer in the character and at the time of her death.
Boudioni, M., McPherson, K., Moynihan, C., Melia, J., Boulton, M., Leydon, G., and Mossman, J. 2001. Do men with prostate or colorectal cancer seek different information and support from women with cancer? *British Journal of Cancer,* 85 (5): 641–648.	Although no pattern between men and women was distinguished with this study, the researchers found that among male colorectal cancer patients, employed men were less likely to request site-specific information, and more likely to need emotional support than retired men. Also that labors were more likely to ask for information about specific therapies then nonlabors.
Brodie, J. 2001. Helplines. Getting through. *Health Service Journal,* 17 May 2001, pp. 26–27.	This study looked at the persistence of callers to reach a live voice on a helpline. It found high persistance in those who eventually did get through, and it found that the launching of a related website did not decrease the number of helpline calls.
Boudioni, M., McPherson, K., Mossman, J., Boulton, M., Jones, A.L., King, J., Wilson, E., and Slevin, M.L. 1999. An analysis of first-time enquirers to the CancerBACUP information service: Variations with cancer site, demographic status and geographical location. *British Journal of Cancer* 79 (1), 138–145.	This was a retrospective comparison of cancer incidence data and,where relevant, population data of first-time users (patients, relatives, and friends) of a the CancerBACUP service. Statistically significant differences were found in the observed and expected sex, age, employment status, socioeconomic class, and geographical location of those calling for the first time. They received much higher than expected calls asking about brain, testis, and breast cancers and non-Hodgkin's lymphoma and calls about bladder, lung, stomach, and colorectal cancers were much lower than expected.

exploration of their data by making a small sample of their data available on their website.

More recently, Cancerbackup has expanded their services to include face-to-face local centers, staffed by cancer nurses, in hospitals throughout the UK. The program is considered successful as it provides direct information and support for approximately 50,000 cancer patients, survivors, and their families through e-mail, phone contact, or letter annually. The website reports 3.7 million pages viewed each month. Specialized oncology nurses provide information and support are, in turn, supported by 200 cancer specialists to ensure the nurses are providing the highest quality information. Cancerbackup is entirely supported by voluntary donations, trusts, corporate sponsorship, special events, publications, and investment income. In 2004, they raised $9,217,700 (US$), spending only $7,349,800 (US$). Their income and assets has steadily grown since program start up in 1999.[41]

Another national program in the United Kingdom, is CancerSupportUK, directed at all levels of cancer care including the longer-term follow-up survivors require. This program was funded by The Diana, Princess of Wales Memorial Fund Project, and is based at the Royal Marsden National Health Service Trust. Its goal is to establish and maintain information and programs for individuals affected by cancer. They undertook collaboration with local organizations to evaluate how the quality of care and support for people with cancer in the community could be enhanced. Special care was taken to address the needs of those, who for example, may have social or cultural reasons, have found access to services difficult. The organizers hoped to reach out to those with cancer, their family and friends, and professional caregivers who many benefit from local resource information. Currently, there is no research reporting on the effectiveness of their programming.

To meet one of their objectives, CancerSupportUK hosts a website (http://www.cancersupportuk.nhs.uk) that explains the interdisciplinary team of professionals that individuals diagnosed with cancer can expect to see within the UK. The team should be comprised of the full complement of caregivers including general and specialized physicians, radiologists, psychologists, chaplains, social workers, dietitians, occupational and physical therapists, nurses, and speech-language pathologists, as well as complementary and alternative medicine practitioners, for the acute stages, but then the website broadens its role to guide the survivor to integrate into the community and support independent living. These community services are provided by Primary Care Trusts to provide high-quality community health services for people living within a defined local geographical area. The CancerSupportUK website hosts links to many community services, explaining how they may be helpful to those living with cancer. Although the program was established with specific goals to evaluate care and support in the community, reports of any evaluations are not yet available for the general public.

Whereas programs like those in the UK are being implemented data on outcomes need to be collected. Also, these approaches are not always easily translatable for other countries, even in the developed world as researchers in Australia report.[42] The multidisciplinary team concept used in the UK where all of the team members come together for face-to-face meetings on a weekly basis would not always work in vast counties like Australia given the great distance between urban and rural communities and the lack of specialists at all locations; 30% of female Australian breast cancer survivors live in remote or rural areas.[42] Furthermore, because Australia's health care system is comprised of many different delivery settings, urban and rural, providing a variety of types of care and had a lack of availability of specialists throughout all regions, previously had financial disincentives for multidisciplinary team meetings.[43] Therefore, a National Multidisciplinary Care Demonstration Project (NMCDP) was initiated in February 2000 in three multifacility collaborations to explore a more flexible model that could be implemented to accommodate the special circumstances of Australia. The same theme of multidisciplinary care (MDC) core principles, *The Principles of Multidisciplinary Care* (Table 4) were used in this model as were used in the UK's models: the critical aspects of a team approach, the need for clear and

Table 4. The Principles of Multidisciplinary Care

Principle of care (Team)	Outcome
• The disciplines represented by the "core" team should minimally include surgery, oncology (radiation and medical oncology), pathology, radiology, and supportive care. The individual woman's general practitioner will be part of her team.	• The "breast cancer care team" is established and known.
• In order to ensure that the woman has access to the full range of therapeutic options, the "core team" may be expanded or contracted to include services (which may be off site), such as genetics, psychiatry, physiotherapy, and nuclear medicine.	• Referral networks established for noncore team specialist services.
Communication	Outcome
• A communications framework should be established which supports and ensures interactive participation from all relevant team members at regular and dedicated case conference meetings.	• Communication mechanisms are established to facilitate case discussion by all team members.
• Multidisciplinary input should be considered for all women with breast cancer; however, not all cases may ultimately necessitate team discussion.	• A local protocol is established for deciding which cases may not require team discussion.
Full therapeutic range	Outcome
• Geographical remoteness and/or small size of the institution delivering care should not be impediments to the delivery of multidisciplinary care for women with breast cancer.	• Systems are established for ensuring that all women have access to all relevant services.
• The members of the team should support the multidisciplinary approach to care by establishing collaborative working links.	• Systems are established to support collaborative working links between team members.
Standards of care	Outcome
• All clinicians involved in the management of women with breast cancer should practice in accord with guideline recommendations.	• Local clinician data are consistent with national benchmarks.
• The treatment plan for a woman should consider individual patient circumstances and wishes.	• The final treatment plan should be acceptable to the woman.
• Discussion and decisions about treatment options should only be considered when all relevant patient results and information are available.	• Final reports are available to all core team members before treatment planning.
• In areas where the number of new cancers is small, formal collaborative links with larger units/centers should give support and foster expertise in the smaller unit.	• Systems are established for the exchange of knowledge and expertise between larger and smaller caseload centers.
• Maintenance of standards of best practice is supported by a number of activities which promote professional development.	• Systems are established for the support of professional education activities.
Involvement of the woman	Outcome
• Women with breast cancer should be encouraged to participate as a member of the multidisciplinary team in treatment planning.	• Women are supported to have as much input into their treatment plan as they wish.

Table 4. (*Continued*)

Involvement of the woman	Outcome
• The woman diagnosed with breast cancer should be fully informed of her treatment options as well as the benefits, risks, and possible complications of treatments offered. Appropriate literature should be offered to assist her in decision making. This information should be made available to the woman in a form that is appropriate to her educational level, language, and culture.	• All women should be fully informed about all aspects of their treatment choices.
• Supportive care is an integral part of multidisciplinary care. Clinicians who treat women with breast cancer should inform them of how to access appropriate support services.	• All clinicians involved in the management of women with breast cancer should ensure that women have information about and access to support services.
• The woman with breast cancer should be aware of the ongoing collaboration and communication between members of the multidisciplinary team about her treatment.	• Women with breast cancer feel that their care is coordinated and not fragmented.

Source: Zorbas *et al.*[42]

frequent communication, access to all necessary care, nationally accepted standards of care including coordination of that care, and the involvement of the individual with cancer through active and timely dialogues with team members. Although the program was designed for women with breast cancer, it was acknowledged from the beginning of the program, that the principles could be applied to other cancers as well.[44]

The NMCDP was implemented to investigate the impact, cost, and willingness of three multifacility sites (called "collaborations") to accept an MDC program for women with breast cancer. Each of the collaborations were allowed to identify MDC strategies that would work within their local environments as long as they were in accordance with the overall *Principles of Multidisciplinary Care.*[43] Collaboration 1 was comprised of an urban area and the surrounding rural areas extending to a state border and including three main rural towns. Collaboration 2 was comprised of five sites distributed over a large geographical area of one state. Collaboration 3 included facilities from several regions within one state, also including a major metropolitan city and two large rural centers.

Collaboration 1 chose to use three strategies to implement in their model:

1. Continued development of an existing breast clinic to create a forum; and move MDC from just the treatment phases, but to include any point beyond diagnosis.
2. Development of a multidisciplinary clinic in another site and to enhance communications. Implementation of a case conferencing system throughout the region using existing information technology.
3. Coordination of breast care nursing and removal of institutional barriers to promote more uniform practice and continuity of care.

Collaboration 2 chose to implement over 40 strategies. They ranged from very specific, such as creating team letterhead to others that were very general such as enhancing current relationships within its region. Their strategies clustered into four main areas

1. Development of an identifiable multidisciplinary team and to bolster the interaction between the team members by:
   - creating and supporting a "team" concept;
   - developing and implementing a clinical management pathway to be able to examine interdisciplinary interaction;
   - conducting group meetings and team sessions for team building and to decrease fears of losing an individual clinical identity by clinicians; and
   - standardizing referral forms and recording outcomes of patient referrals.
2. Instituting regular case conference team meetings, linking nonlocal sites with videoconferencing.
3. Developing or strengthening collaborative relationships across the region by:
   - assessing current deficits in service provision;
   - creating a directory of off-site services; and
   - developing shared-care processes to limit the amount of required patient travel.
4. Ensure all newly diagnosed women have the opportunity to speak with a supportive care team member before treatment decisions are made. This was accomplished through developing specific protocols.

Collaboration 3 chose several strategies that can be placed into three main areas:

1. Identifying a breast care nurse to:
   - become a member of the multidisciplinary team and attend case conference meetings, giving feedback to the patient and family of the meeting outcomes;
   - promote seamless coordination of care, information, and referrals through the phases of diagnosis, surgery and adjuvant therapy; and
   - develop and/or strengthen relationships between the collaborating sites by attending satellite clinics and creating formal linkages with relevant nursing staff.
2. Focus on enhancing communication within the multidisciplinary team by discussing all cases including patients from rural areas in the network.
3. Develop either video or teleconferencing linkages with the rural centers in the networks to allow their participation in multidisciplinary meetings.

The project was evaluated with feedback from the participating clinicians and from the cancer survivors. Collaborations 1 and 2 sought to increase the role of the general practitioners in the MDC meetings, but only Collaboration 1 was successful with their strategies to have consistent involvement of those clinicians. Collaboration 3 reported the highest pre- to post-implementation changes of the collaborations—this collaboration had included a specialist breast care nurse to help coordinate care, and also attempted to create linkages with rural centers. With a psychologist as also attending some of the Collaboration 3 meetings, the evaluation team felt that it was the increased focus on the psychosocial issues that mostly contributed to the overall high program outcomes. Survivors identified the critical function of consistent communication among the team members, particularly noting that some confusion came when the professionals communicated conflicting information to a patient acting as if the professionals themselves were not communicating.

Activity logs and clinical audits were made to follow attendance at team meetings in an attempt to gather some objective data on the clinical care. It was reported by the evaluators that the project was too short and had too few women to demonstrate clear clinical outcomes; therefore they did not chose to report them. However, project costs were tracked and reported. These are presented in Tables 5, 6, and 7. The goal of

Table 5. Cost Summary for Collaboration 1 of an Urban Area and the Surrounding Rural Areas Extending to a State Border and Including Three Main Rural Towns

Cost summary for Collaboration 1

	Cost item	Baseline (6 months)	Start-up (8 months)	Implementation (7 months)	Post-implementation (6 months)
A	Staff attendance at treatment planning meetings[a]	*Nil*	3, 222.35	25, 614.31	31, 766.79
B	Capital and equipment[b]	No data	11, 500.00	379.50	0.00
C	Teleconferencing[c]	No data	0.00	0.00	0.00
D	Meeting organization[d]	No data	5, 316.85	4, 652.25	3, 987.64
E	Other meeting-related costs[e]	No data	1, 244.18	1, 307.41	970.63
F	Total cost of education meetings	16, 072.29	9, 749.30	15, 439.65	9, 730.51
G	Breast care nursing (nonmeeting)[f]	No data	0.00	0.00	4, 049.27
H	Project manager/ coordinator[g]	No data	19, 055.73	16, 673.77	14, 291.80
I	Staff personal time[h]	No data	34, 916.00	18, 538.00	15, 548.00
J	Travel and accommodation[i]	No data	1, 036.02	906.52	777.01
K	Other costs[j]	No data	4, 407.28	1, 333.89	1, 143.33
L	Total costs per phase	16, 072.29	90, 447.71	84, 845.30	82, 264.98
M	Total meeting costs (A+B+C+D+E)	0.00	21, 283.38	31, 953.46	36, 725.06
N	Number of treatment planning meetings (number of sites)	0	2(1)	21(2)	23(2)
O	Average staff attendance cost per meeting (A/N)	0.00	1, 611.17	1, 219.73	1, 381.16
P	Average total cost per meeting (M/N)	0.00	10, 641.69	1, 521.59	1, 596.74
Q	Number of patients	No data	4	49	58
R	Average total meeting costs per patient	No data	5, 320.85	652.11	633.19
S	Number of cases presented	No data	4	56	67
T	Average staff attendance cost per case presented (A/S)	No data	805.59	457.40	474.13
U	Average total meeting cost per case presented (M/S)	No data	5, 320.85	570.60	548.14

Information from log book and supplementary data where specified.

[a] Baseline calculated from information provided on Baseline costing study sheets.

[b] From project budget summary: $13,956.74 spent on secretarial wages for entire project. Pro-rated.

[c] Includes the costs associated with room hire, food, and catering, from logbook data. Catering of $2872.22 from project budget summary pro-rated.

[d] The breast care nurse salary of $9500 (project budget summary), less breast care nurse meeting attendance (log book).

[e] From project budget summary: $50,021.30 spent on local evaluator wages for entire project. Pro-rated.

[f] Collaboration retrospectively estimated personal time. Costed at appropriate salary rates.

[g] Log book data ($0) and project budget summary: $619.55 travel costs and $2100 project worker costs. Pro-rated.

[h] From project budget summary: stationery $4001.66 pro-rated equally; advertising ($880.75+706.75), education ($732) and incorporation ($563.34) assumed to occur in start-up.

Table 6. Cost Summary for Collaboration 2 of Five Sites Distributed Over a Large Geographical Area of One State

Cost Summary for Collaboration 2

	Cost item	Baseline (6 months)	Start-up (8 months)	Implementation (7 months)	Post-implementation (6 months)
A	Staff attendance at treatment planning meetings[a]	15, 500.40	15, 488.94	30, 954.72	32, 167.42
B	Capital and equipment[b]	No data	0.00	328.46	281.54
C	Teleconferencing[c]	No data	938.66	765.06	231.48
D	Meeting organization[d]	No data	5, 300.05	4, 694.33	3, 937.18
E	Other meeting-related costs[e]	No data	100.00	0.00	0.00
F	Total cost of education meetings	No data	11, 905.69	4, 897.69	4, 964.09
G	Breast care nursing (nonmeeting)[f]	No data	0.00	0.00	0.00
H	Project manager/ coordinator[g]	No data	14, 898.55	39, 227.88	33, 703.30
I	Staff personal time[h]	No data	22, 130.50	9, 800.65	0.00
J	Travel and accommodation[i]	No data	0.00	1, 753.27	1, 520.80
K	Other costs[j]	No data	4, 644.81	1, 741.30	1, 492.54
L	Total costs per phase	15, 500.40	75, 407.19	94, 163.36	78, 280.35
M	Total meeting costs (A+B+C+D+E)	15, 500.40	21, 827.65	36, 742.57	36, 617.62
N	Number of treatment planning meetings (number of sites)	24	31(3)	59(3)	43(3)
O	Average staff attendance cost per meeting (A/N)	645.85	499.64	524.66	748.08
P	Average total cost per meeting (M/N)	645.85	704.12	622.76	851.57
Q	Number of patients	No data	82	186	155
R	Average total meeting costs per patient	No data	266.19	197.54	236.24
S	Number of cases presented	No data	109	231	198
T	Average staff attendance cost per case presented (A/S)	No data	142.10	134.00	162.46
U	Average total meeting cost per case presented (M/S)	No data	200.25	159.06	184.94

Information from log book and supplementary data where specified.

[a] Baseline calculated from information provided on Baseline costing study sheets.

[b] From financial statements $610 spent on equipment during implementation and post-implementation period. Prorated.

[c] From financial statements $732.41 spent on telephone and fax during start-up and $501.54 during implementation and post-implementation period. Cost in latter two periods is pro-rated.

[d] Cost based on 0.5 day registrar time +1 hour secretarial support.

[e] Includes the costs associated with room hire, food, and catering, from logbook data.

[f] The breast care nurse cost was pro-rated using "salaries" $14,982.22 during start-up and $73,023.82 during implementation and post-implementation from the financial statements less breast care nurse meeting attendance (log book).

[g] May form part of "salaries" amount listed under breast care nurse.

[h] Based on estimate of personal time by senior clinician; costed at appropriate salary rates.

[i] Log book data ($0) and financial statements $3256.07 travel costs. Pro-rated between implementation and post-implementation.

[j] From financial statements. During start-up: $4348 overheads and $296.81 other; during implementation and postimplementation: overheads $1739.14, printing and copying $679, and consumables $815.70 (other of $244.35 assumed to have been counted in start-up). Cost in latter two periods is pro-rated.

Source: National Breast Cancer Centre.[43]

Table 7. Cost Summary for Collaboration 3 of Several Regions Within One State, Also Including a Major Metropolitan City and Two Large Rural Centers

Cost Summary for Collaboration 3

	Cost Item	Baseline (6 months)	Start-up (8 months)	Implementation (7 months)	Post-implementation (6 months)
A	Staff attendance at treatment planning meetings[a]	13, 206.55	17, 688.37	14, 098.71	12, 571.10
B	Capital and equipment[b]	No data	0.00	0.00	0.00
C	Teleconferencing[c]	No data	0.00	0.00	0.00
D	Meeting organization[d]	No data	4, 426.10	3, 920.26	3, 287.96
E	Other meeting-related costs[e]	No data	0.00	0.00	0.00
F	Total cost of education meetings	No data	0.00	1316.65	544.56
G	Breast care nursing (nonmeeting)[f]	No data	47, 401.76	41, 476.54	35, 551.32
H	Project manager/ coordinator[g]	No data	0.00	0.00	0.00
I	Staff personal time[h]	No data	2, 631.80	0.00	0.00
J	Travel and accommodation	No data	572.70	1, 316.65	0.00
K	Other costs	No data	10.00	0.00	0.00
L	Total costs per phase	13, 206.55	72, 730.73	62, 680.84	51, 954.94
M	Total meeting costs (A+B+C+D+E)	13, 206.55	22, 114.47	18, 018.97	15, 859.06
N	Number of treatment planning meetings (number of sites)	26	25(1)	25(1)	20(1)
O	Average staff attendance cost per meeting (A/N)	507.94	707.53	563.95	628.56
P	Average total cost per meeting (M/N)	507.94	884.58	720.76	792.95
Q	Number of patients	No data	90	104	86
R	Average total meeting costs per patient	No data	245.72	173.26	184.41
S	Number of cases presented	No data	103	110	89
T	Average staff attendance cost per case presented (A/S)	No data	171.73	128.17	141.25
U	Average total meeting cost per case presented (M/S)	No data	214.70	163.81	178.19

Information from log book and supplementary data where specified.

[a] Baseline calculated from information provided on Baseline costing study sheets.

[b] This cost was not recorded but is estimated using the methods described in the report.

[c] Includes the costs associated with room hire, food, and catering.

[d] The breast care nurse salary of $5925.22 per month (report) less breast care nurse meeting attendance (from log book =$0). Higher than actual costs as a more senior nurse rate has been used.

[e] Not employed.

[f] Collaboration estimated personal time during teleconference. Costed at appropriate salary rates.

[g] From ledger summary: $1050 travel from 8/00-6/01 (pro-rated at $95.45/month) and $839.40 from 8-9/01.

[h] From ledger summary: $10 for stationery, assumed to be during start-up.

the economic analysis was to estimate the costs for the set-up and implementation of MDC strategies, with a focus on establishing and maintaining MDC case conference meetings; they were not attempting a cost-effectiveness analysis.

As expected by the evaluators, because of the variance in the number of meetings, conferences, the number of attendees, and baseline differences, the cost differences between collaborations were varied. For example, in Collaboration 3, team meetings had already existed, so the average cost by the end of the project was approximately $800 per meeting (or $180 per case presented), but in Collaboration 1, where team meetings needed to be established, the average cost of the team meeting at the end of the project was approximately $850, or approximately $236 per case presented. Every collaboration had higher cost reported in the start-up phases, for example, Collaboration 1 needed to purchase videoconferencing equipment and Collaboration 3 had to hire a breast care nurse specialist, but over time some cost did decline.

This NMCDP was evaluated again in 2004 to assess the project's ability to sustain its efforts after it was through the demonstration phase.[45] The team of evaluators found that while the program was being implemented as planned, there were areas for improvement generally related to adherence to the program principles such as completing weekly case conferences, and the need to reorient team members to the program ideals including reminders of the importance of the weekly team conferences consistently occurring, the support for the necessary infrastructure. Some resistance to change by the professionals was noted as well as some fear of loss of clinical independence.[44] A suggestion was made to enlist the help of an clinical team member "champion" to help drive the process. The evaluators also noted the importance of continued allocation of funding to sustain the program. Also, even though the demonstration project did highlight some benefits to the women with breast cancer of the MDC model, such as the benefits of enhanced support and communication, it was recommended by the project evaluators that clinical outcome studies be undertaken to establish the benefits of MDC for patients with other cancers, creating an evidence base for the widen application a MDC model.[43]

Other nations have also implemented cancer care programs to address the multifaceted needs of the cancer patient. One such model is called the "shared cancer care program" tested in Denmark whereby the responsibility for the long-term health care follow-up of the cancer patient was to be shared between individuals or teams who are part of separate organizations, or within organizations where considerable boundaries exist.[46] This program was aimed at helping patients to break the solitary tie to the oncology specialists in favor of a more shared vision of care with other practitioners, particularly general practitioners.

The shared care program had three elements: (1) knowledge transfer; (2) communication channels; and (3) active patient involvement with more direct communication occurring with the patient's primary care provider and the cancer treating specialists. Figure 2 details the components of each section of the shared care program. This project was tested using randomized control trial methodology with patients randomized into an intervention and a control group. The control group received routine care, but the study subjects received enhanced communication and their treating clinical team shared information more forthrightly. The project required detailed discharge summaries prepared for the end of the treatment period complete with a detailed description of care to date, instructions for further care, and documentation of the information the patient received. The summary also touched on any physical, psychological, and social problems that the patient had, or was expected to get over time. Names and phone numbers of doctors and nurses who worked with the patient were listed for ready reference for all. Patients were told information would be sent to the general practitioners (GPs) and that they could call those physicians with any problems that arose.

Shared Care Program

Knowledge Transfer

- Discharge summary letters following predefined guidelines
- Specific information on the disease and its treatment
- General information about chemotherapy
- General information about radiotherapy
- General information about pain treatment
- Information about treatment of induced nausea and sickness
- Information about some acute oncological condition

Communication Channels

- Names and phone numbers of doctors and nurse responsible for the patient were attached to the discharge summary letter to the GP's

Active Patient Involvement

- In the intervention group, the patience received oral as well as written information about the information package to their GP
- The patients were encouraged to contact their GP when facing problems they assumed could be soled in this setting

Figure 2. Shared Care Program. *Source*: Nielsen *et al.*[46]

Outcome measures for the study addressed the patients' attitude toward the health care services, reports on contact with the GP, and health-related quality of life and performance status. Subjects were followed for 6 months, but were assessed at baseline, 3 months, and 6 months. Evaluation of the program has found it to be successful with respect to patients feeling less like they were in "limbo." At 6 months the men in the intervention group felt less in limbo ($p = 0.031$) as did the younger (18–49 year olds) age group at both the 3-month and the 6-month follow-up ($p = 0.024$ and $p = 0.031$, respectively) than those in the control group. Patients in the intervention group made more contact with their GPs than did those in the control group. It was interesting that the researchers noted that for the men in the intervention group, with men being more likely to not reach out, that the men contacted their GPs as often as the women did. No differences in health-related quality of life were noted between the two groups, meaning that if the individual is in a shared care program, he or she will most likely not report a negative impact on health-related quality of life.

The program involved professional training, the buy-in of GPs to broaden their role to assist with direct follow-up of the oncology care, and reimbursement. The researchers admitted that having the oncologists write more detailed discharge summaries was one of the most challenging components of the program. This process was new in the doctors' routines, and they had to be written and mailed on the day the patient was discharged from the department or outpatient setting. As the department was used to conducting randomized controlled trials, they were used to following guidelines such as the one that scripted the discharge summary. Further support was offered for follow through on the project by the fact that the department felt ownership for the project and a head group of consultants impressed the importance of the project onto the clinicians to follow the protocol. However, the most essential support was that one of the researchers tracked the project daily, leading and encouraging the progress. The project used a GP as this key lead to help bridge between the oncologists and the GPs.

Other countries have also tried to reduce the reliance on the oncologist as the primary source of care for long-term follow-up. In England, a randomized controlled study of lung cancer patients found that follow-up by nurses over cancer care specialists had a high acceptability of the nurse-led follow-up with 75%(203/271) of eligible patients consented to participate "accepting" the nurse over an oncologist.[47] The project sought to compare traditional medical follow-up where by the patient is seen at 2 or 3 month interval in a clinic, or more often as needed, for medical assessment and to monitor disease progression. The nurse-led follow-up program allowed clinical nurse specialists to follow up with the patient either over the phone or in a clinic for medical follow-up and assessment. The nurses were prepared for their study role by observing outpatient lung cancer clinics and shadowing medical consultants. Patients were able to contact the nurses at any time and could go in for follow-up at the clinics without appointments. In addition to the medical care, the nurses broaden their roles to offer support, referral to community agencies, and coordination of input between agencies. Nurses were to follow patients for signs of disease progression, symptoms that may need attention, and any other serious complications that may arise.

Patients in the intervention group with the nurse-led follow-up reported less severe shortness of breath at 3 months into the study and higher quality of life ratings as measured by European Organisation for Research and Treatment of Cancer's (EORTC) core questionnaire about quality of life and module about lung cancer. No significant differences in the GPs' overall satisfaction were seen between the control and the intervention groups. Overall, 26 (18%) of the GPs in the study stated that they would prefer nurse-led follow-up for future patients, 13 (9%) would prefer follow-up by an oncologist alone, and 66 (46%) would prefer follow-up by an oncologist and nurse specialist. Whereas costs were originally to be considered part of this study, in the end it was difficult to separate out the time spent by nurses and physicians between study activity and was a part of their daily service, although analysis of the data they were able to use found no significant differences in the costs of the nurse-led program to the conventional or control follow-up. Costs for 3, 6, and 12 months of nurse led care (£222/$370US;£370/$660US; £ 670/$1,195US) were less than conventional care (£229/$515 US; £364/$649US; £750/$1,328US).

Canada has also made some modifications in their cancer care programming to increase the use of primary care over specialists for follow-up care, to reduce reliance on the more expensive specialists and to increase ongoing care into the community. A mail survey of a random selection of patients in Manitoba was conducted to inquire about their care use at 6 and 12 months after diagnosis revealed that 10% of the women had mostly specialist care for all medical needs, and 44% had parallel care where they used specialists for cancer care and family practitioners for all other medical care, and 39% used shared care where *both* doctors took care of cancer-related care, and the family practitioner followed for all other general medical needs. Study participants felt that the role of the family practitioner was diminished after diagnosis, although specialty care is needed, both family practitioners and patients need to be aware of the valuable contributions the family practitioners could make in follow-up care. The role of specialty clinical for survivors and the training of primary care providers to expand their care of cancer survivors is a very important area; program development and research will ideally guide these activities.

Regional cancer centers in Calgary Canada have recognized this important role as regional experts and have intervened to support the role of the local community family practioner,[48]such as using a standardized letter template to prompt for inclusion of specific details, recommendations, and contact information for the specialist to use to communicate with family practitioners to hone communication between these two professionals to enhance patient care, similar to the letters to be provided for patients in the Lance Armstrong Foundation Living Well After Cancer project described in an earlier chapter in this book. The study was evaluated in terms of the satisfaction with the consultation letters (comparing routine one in place to the new standardized letter) with respect to their relevance, timeliness, consistency, format, amount, and general satisfaction, and how satisfied the family physicians were with their clinic notes before and after the use of the standardized template letter. A 55% response rate was achieved; overall general satisfaction with the template letters was significantly increased over the nonstandardized letters used previously. The same was found for all aspects of the satisfaction with the clinic notes. After the study's implementation, family physicians reported a shift from 10% satisfaction with their notes to a 60% satisfaction. This increase in amount, type, and frequency of communication has extended the expertise of the regional center into the community in the more rural areas of Canada.[48] Further studies need to address the impact on actual patient care, specific outcomes, and satisfaction with services.

The Princess Margaret Hospital in Toronto, Canada offers a survivorship program for those with breast cancer. They offer a free booklet, entitled Getting Back on Track: Life After Treatment, funded by a grant from the Canadian Breast Cancer Foundation—Ontario Chapter, that provides information on what to expect when the acute phase of treatment is over. Also, $2 million was committed in 2004 to establish a Survivorship Clinic and Program to address the physical and psychological needs of breast cancer survivors, and broadening to include all types of cancer.

With the theoretical underpinning of active patient empowerment and The Expert Patient Program, the survivorship clinic's three main program goals include being a forum to encourage peer support, helping survivors create plans for ongoing support and empowerment to assist them in their reintegration, and to increase their quality of life as they transition through the phases of treatment into survivorship. The program begins for the survivors immediately after diagnosis with support and education. The program offers opportunities for face-to-face interaction, well as Internet and phone support. They are also working with the community to link with established support organizations to help bridge the gap from the hospital for the survivors. This is Canada's first comprehensive cancer survivorship clinic and program,[25] with formal enrollment just getting underway. Outcomes to be measured include components of quality of life such as stress, distress, and anxiety reduction with goals to develop an empowerment scale along with longitudinal outcomes studies including biological and economic aspects.

A unique aspect of this Canadian program is that survivors are partners in the acute care hospital whereby electronic medical records are made accessible to the survivors. As a phase of training for empowerment, survivors are encouraged to review lab results prior to clinic visits to prepare better questions for their clinical team and to be aware of their own care processes. The program also utilizes peer support volunteers in many areas of the programming. Volunteers must be at least 1 year into their survivorship. The program has future directions to include online support groups and planning for its ongoing funding. As the program is both academic as well as clinical, the program will seek research grants and build on the support of hospital administration on extended care models to cover some of their costs under the auspices of the hospital care program. This program needs to be systematically evaluated.

Looking toward Australia, that nation, as in many developed countries have shifted their focus of treatment of the cancer patient from being mainly the responsibility of the oncologist to use of a professional team including oncology, pathology, radiology, supportive care services, and the patient's general practitioner along with key significant others. The National Breast Cancer Centre and the National Cancer Control Initiative in Australia has developed national practice guidelines that include care following the diagnosis, but also for survivors, focusing on the common physical, psychological, and psychosocial issues that arise for survivors as identified in the literature. Adherence to these guidelines and methods to improve adherence and related outcomes represent important next steps in development and evolution of such programs.

Japan's cancer program, although well-funded, has not yet shifted its focus to cancer survivors. By 1981, Japan was reporting that cancer was the leading cause of death for their nation. In 1997, Japan's Ministry of Health and Welfare, the Ministry of Education, Science, Culture and Sport, and the Science and Science Technology Agency Cancer had provided nearly 6200 million yen (Nearly $50,000,000 US) for cancer research related to early detection, prevention, the development of new diagnostic technologies and therapies, and on the quality of life of cancer patients,[29] with no money specifically being earmarked for the study of cancer survivors. Although scientifically rigorous, even the mission of the Japanese Clinical Oncology Group is still directed at improving the standard treatment of cancer by carrying out large, prospective, randomized, multicenter, clinical trials,[49] rather than address the ongoing needs of the survivor.

Similar to Japan, China is intently focused on cancer prevention and the promotion of healthy lifestyles, but also has not undertaken a systematic approach to the study of survivors. China suffers from a significant lack of health care resources available to the rural population in order to provide any level of treatment for those with cancer, therefore, cancer survival rates are low in these areas.[50] Currently, the goals for China as a nation are to prevent and treat cancer with respect to their cultural needs.

Programs in most of the developed world are not as well planned, organized, or funded as the programs in the UK, Australia, or Canada, or the one supported by the Lance Armstrong Foundation described earlier in this book. Most programs in these countries began in the late 1950s or early 1960s. Most are charitable NGOs and are run by lay individuals, with or without professional supervision. They do not collect data, nor do they test their impact on the populations they are surviving, however they do provide support, some basic patient education, and referral to other programs and services. For example, in Thailand, The Bangkok Breast Cancer Support Group is comprised of over 20 volunteer women who've had personal experience with breast cancer. They strive to provide emotional support both to each other, and to women who've been recently diagnosed with breast cancer. Most of the links on their website are to support agencies within the United States. Likewise, Jamaica offers similar programming with their Reach to Recovery program, a group of breast cancer survivors, friends and well- wishers who meet monthly. Their primary goals are to: (1) Increase public awareness of breast cancer and advocating for early detection to increase the chance of long productive lives; and (2) Provide a self-help group with emotional and psychological support to breast cancer survivors, their families and friends. Again, lay leaders who are survivors themselves, although several of their members are professional counselors, run Jamaica's support groups.

Romania, through an NGO, The Romanian Cancer League, also provides education and support, but they strive to include members of the patients' professional medical team including psychologists, oncologists, priests, and other patients and their families. Since 2001, the Romanian Cancer League has lead the celebration of Cancer Survivors' Day on December 21. This celebration was designed to give survivors a "reward" for their journey in which they receive theater tickets and gifts to "help make them feel important and happy."[48] The Cancer League is funded through a variety of sponsors including pharmaceutical companies, medical device manufacturers, private foundations, banks, and investment companies.

Singapore also takes an additional step with their general support programming through their NGO to extend services to include financial assistance, ongoing support for survivors, and rehabilitative care. The Philippine's Cancer Society, also now an NGO, takes another step by including education and information, services such as support, pain relief, and consultations, but they also include research as part of their mission to address all levels of cancer control. The Society is lead by a board of directors made up of seven lay individuals and eight doctors who are elected to their positions on an annual basis. It is funded through membership dues, donations, and contributions to annual fund campaigns. It receives no governmental subsidies.

Ireland's Cancer Society, is the national charity dedicated to preventing and treating cancer, and seeks to improve the quality of life of survivors through patient care research and education. They offer the FreeFone Cancer Helpline that is staffed by fully qualified nurses which receives approximately 7000 calls annually on topics concerning cancer prevention and screening to diagnosis and treatment. The line is used by survivors, their significant others and health care professionals. Again this organization is an NGO, but has professional staffing.

The developing countries are reliant on the more developed world for support and assistance with their cancer burden, particularly through efforts of the WHO. The WHO works with and through the NGOs in nations across the word to provide resources, direction, and support. Most of the Third World nations do not even offer much in the way of support services such as the informal services offered in Jamaica, Latin America or Thailand. Sierra Leone, reputed to be the one of the second poorest countries in the world and be among those countries with the lowest life expectancy rates,[51] is not even able to provide chemotherapy. Additionally, survival among women with cervical cancer in Latin America and the Caribbean is poor because women in these cultures reach out for care very late and when they do the treatment they receive is insufficient and supportive care is nearly absent.[52] In Turkey, the field of oncology has been struggling to become established. According to the International Society of Nurses in Cancer Care, the area of oncology nursing is not even part of a formal educational program, certification process, or offered in continuing education courses. There was a graduate oncology nursing program that started in one of the universities in 1995 which, but it is not currently active, and the program has only graduated one nurse. Still in other countries even this much progress has yet to be made, as in Africa, were efforts to manage the AIDS epidemic and general public health issues are taking precedence.

Some programs are trying to take on a global mission, even beyond the efforts of the WHO. The International Cancer Information Service Group (ICISG) seeks to move the more informal types of support services to an international level. A Cancer

Information Service is the program to provide current information for survivors, their families, and health professionals. The ICISG goals include:

1. The promotion of international collaboration among Cancer Information Services.
2. The sharing of information and tools for management, evaluation, training, and quality.
3. Serve as a forum for exchange and discussion.
4. Create and update service minimum standards.
5. Promote awareness of Cancer Information Services.
6. Encourage and support the development of new services throughout the world.

Members of this organization are entire countries, with the US considered currently the sole expert member. The benefits of membership include having the access to, and the sharing of resources, the inclusion in a forum to share knowledge, skills and to network, and access to a listserv of other members. The ICISG offers an assessment tool (Figure 3) to facilitate the assessment of organizational capacity to establish and host a Cancer Information Service.

Furthermore, the International Union Against Cancer (UICC), the largest independent, nonprofit, nongovernmental association with more than 270 cancer-fighting organizations in over 80 countries seeks an advocacy role as well as a research role. Members of this organization include ministries of health, in some countries, and in others they are voluntary cancer leagues and societies, and cancer research and treatment centers. UICC promotes directed communication and collective action to support a global campaign against cancer, including advocacy groups, patient survivor support networks, voluntary cancer societies, public health professionals, and research and treatment centers. The mission of the UICC is multifaceted into the areas of prevention and early detection, and in the promotion of the campaign against cancer internationally. For example, Reach to Recovery International (RRI) is an international support program for the newly diagnosed, as well as survivors, to receive ongoing information about cancer, to provide opportunities for volunteering to support the newly diagnosed patient, and to promote services. RRI is a program sponsored by the UICC focusing on breast cancer and supports a biannual conference and a semiannual newsletter, all with a focus on international support and exchange of information. The association also supports the World Cancer Day that is an annual reminder of the international needs in cancer care and survivorship. The programming of the UICC is supported through the International Cancer Foundation Endowment. It seeks donations so it can provide long-term reliable support.

7.0. FUTURE DIRECTIONS

Throughout the last century the focus of health care has moved from an acute care model to a chronic disease model as medical science and technology have advanced, however, this transition has not occurred at a uniform pace across the globe. Some nations, particularly the developing countries, are still grappling with primary medical care needs and basic public health concerns such as sanitation, infection control, and poverty. This means then that the risk of cancer and the ability to survive and address the problems of survivors is widely variable across

Conduct a Basic Overview Assessment
Assess the user/audience, the environment (i.e., what else exists), and the capacity of the sponsoring organization:
Users Audience
Geographic area to be covered

- Demographics of audience
- Population base
- Male/female
- Ages
- Income
- Education
- Major languages spoken
- Cancer incidence by type
- Culture/tradition/beliefs about cancer

Environment

- Extent of present information services (face-to-face, telephone, Internet, other)
- Existing information sources
- Competing programs and services

Capacity of Sponsoring Organization
Gaps analysis, briefly describing the need and who can best fulfill it

- Services available with whom to collaborate
- Anticipated major barriers and how to overcome them
- Potential funding sources and anticipated budget/amounts

Describe Scope of Services That You Would Like to Offer
Describe the type of services you would like to offer and how you want to reach you clients. You should look at the following:

- Potential audiences
- Estimated types of services to be offered
- Information
- Counseling
- Support

Reach your Audience by:

- Telephone
- Internet website
- In person
- E-mail
- Mail
- Publications

Other Issues for Consideration:

- Estimated volume for each type of information delivery
- Information depth and sources
- Information updating policies
- Database (information resources and referral) to be used and equipment needed
- Hours of service
- Staffing pattern and training needs
- Qualifications of staff (volunteers, medical personnel, counselors, information specialists)
- Medical referral policies

Figure 3. Assessment Tool for a Cancer Information Service Program. *Source:* International Cancer Information Services Group (http://www.icisg.org/start_assessment.htm)

nations. The majority of the variation is attributed to a range of known exposures and suspected risk factors stemming from the environment or lifestyle choices[1] but also funding and priorities. Internationally, cancer treatment and its subsequent survivorship are promoted or prohibited by individuals' dependency on the levels and types of available treatment and their countries' health care systems, and various economic and sociocultural factors. Unlike the progress that has been made in parts of the United States, Canada, Australia, and in many of the European countries, much of the world is still struggling with detecting and treating cancer, in addition to dealing with substantial other basic public health needs rather than expanding efforts in the direction of cancer survivorship.

Understanding the worldwide extent of the cancer burden is still an ongoing concern. There is a new endeavor seeking to combine the European EUROCARE registries with the United States' and Canada's registries to undertake a trans-Atlantic comparison. The project is entitled CONCORD and results are being reported in phases over this decade. It is hoped that this effort will help further develop practice and policy regarding best practices in cancer survivorship that can be implemented worldwide to reduce disparities and increase quality of life whatever those cultural-specific definitions are.

Much of the focus of early research in cancer on a global basis has been more epidemiological in nature to better understand the patterns of cancer, and more recently causes and treatments have begun to be more prevalent. However, researchers in Europe, Japan, and Australia are just starting to generate studies in the area of quality of life among long-term cancer survivors,[14] but more needs to be completed in this area. More education on late effects of treatment within the survivor population is also required.[14] Additionally, survivorship programming that has been implemented to facilitate reintegration after treatment needs to be systematically evaluated in order to understand impact of the program on the individuals within the program, as well as economic evaluation of the programming to adequately address the costs of establishing and maintaining such program so that if they are found to be effective, these programs can be sustained and grown, if necessary.

Much can be gained through the sharing of information and resources within the global community. Many of the nations with less well-developed survivorship programming were able to find access to programs within the US and the UK valuable, particularly through the use of links placed on websites. In fact, the use of the Internet has created a forum for information sharing on all levels including support, education, information, and data sharing for international cancer-based organizations.

Given that it is projected that 300 million new cases of cancer will be diagnosed over the next 15 years, and over one third of those cases will survive,[53] there is an urgent need for organization and infrastructure much like the European nations have embraced on an international basis. The future holds much opportunity for those who survive cancer, the nations of the world need to continue to position themselves to support these survivors. The methods of interacting with individuals in some countries implemented have proven to need modification in order to maximize success in other nations. The access to and availability of qualified professionals is a key component of a survivorship program, a more definitive list of professional knowledge and skills need to be clarified and research completed to confirm the optimal team makeup. Representing a first step in recognizing the need for more uniform practice guidelines as health care information becomes more globalized, the American Society of Clinical Oncology and the European Society for Medical Oncology has taken a leadership role in the development of "The Recommendations for a Global Core Curriculum in Medical Oncology."[54] The WHO is implementing plans of working within culture parameters by enlisting the support of the NGOs within the various countries.

Individuals are being diagnosed and treated more quickly in much of the world; the next steps need to be on helping survivors better manage treatment side effects, reintegrating survivors into healthy and productive lifestyles, and supporting research efforts on their ongoing needs. Looking toward the future, the global community needs to develop strategies to share the evolving knowledge of survivor programs, particularly as the current programs move to evaluate their own effectiveness. Communication also needs to be enhanced to connect nations with access to necessary professional support to those nations who lack this, as well as to educate the world on what is currently being undertaken to promote innovation and country-specific implementation and evaluation of emphatically supported program components to enhance the use of evidence-based care with survivors. The greater use of web-based technology, the use of handheld computers in some economically advanced countries, as well as the use of traditional forms of communication (e.g., radio programs, newsletters, telephone), could fill gaps. Additionally, funding needs to broaden the WHO's mission to allow the creation of survivorship programs to expand its focus to directly include cancer survivorship programs. Such programs should be tailored to provide culturally sensitive effective resource use while bolstering the individual's ability to navigate his or her own course in collaboration with the professionals and the community.

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Part VI

Future Directions

Chapter 26

Cancer Survivorship

Research, Practice, and Policy

Michael Feuerstein

1.0. THE CHALLENGES

The chapters in this book provide a foundation for current research and practice in many areas that impact cancer survivors. Much of this work has evolved over the past decade with the support of federal agencies, and other public and private organizations around the world. The hard work of many is beginning to come to fruition. Although momentum has significantly increased, particularly in the past decade, it is clearly just the beginning. This early work forms a very important base. However, a new age is dawning. Much more needs be learned, developed, and disseminated to providers, families, employers and survivors. For example, from a clinical perspective it is now recognized that there is a need for a coordinated effort following major cancer treatment. This effort should be spearheaded by the treating oncologist or primary care provider or both. Both groups seem to be vying for this new practice opportunity but from my perspective we need to look at who and how the necessary follow-up services can be best provided and not just "give it" to the most vocal lobby.

Recently, while attending a monthly meeting of brain tumor survivors a fellow survivor spoke about the anxiety she experiences several weeks before her follow-up MRI and medical exam. She had no idea that there are medications she could take or self-management strategies that she could learn that might help her cope more effectively with this quarterly ritual. She was very interested in various options members of the group spoke about. Why didn't one of her doctors, she has many of them, tell her about these options? Are these approaches so rare that they are only known by a few? Do most providers think they are a waste of time and money? The evidence doesn't show that. These anecdotes are all too familiar to survivors and have been discussed by survivors and advocates for years. This story clearly illustrates a problem of case coordination or "cancer survivor navigation" and the lack of awareness by both providers and survivors that there are options.[1] This example involved a very well-educated woman living in a large city with a very supportive and attentive spouse. What about those in smaller towns or rural areas or those not as well-educated or without support persons?

Epidemiology informs us that the number of survivors is increasing and, as was mentioned many times, there is every reason to assume that this will continue upward as more effective early screening and interventions emerge and the population ages.[2] Much remains to be done for these cancer survivors. There is a pressing need for bold new approaches. A systematic public health approach worldwide is one such effort that could move our understanding, prevention, and care of cancer survivors forward in a way that has been accomplished for other acute and many chronic health problems. This effort should be international in scope and comprehensive. While many elements of this type of approach are in their early stages, there needs to be many more highly skilled epidemiologists, health services researchers, exercise physiologists, nutritionists, physician researchers of all relevant specialties, physical and occupational therapists health psychologists and others involved in health care and research working together toward this goal. This cadre of professionals is needed in order to better define the dimensions of cancer survivorship, describe its natural history, by cancer type, treatment, molecular processes, and other variables yet to be defined. We need more comprehensive and representative data on the actual problems of survivors, their temporal patterns and their recurrence. There is also a need for much more precise estimates of survival by type of cancer, age, gender, and ethnicity. We need to take a more serious look at the validity and use of conditional probability estimates a more positive and perhaps accurate look at the "crystal ball" since those diagnosed with cancer are, in fact, living longer.[3]

There needs to be a more evidence based case definition of survivorship that genuinely captures naturally occurring phases of survival based on problems over time, patterns of problems or recovery over time, and/or various critical end points (biological, psychological, and functional). The definitions of cancer survivorship at this point have been useful but they are not based on actual patterns of outcomes or the natural history observed among cancer survivors but rather categories based upon important but personal observation[4] or proposed by a few cancer survivor researchers.[5] These early definitions certainly have been useful, however, it is time to go beyond them and look at natural history data to provide more realistic operational definitions of survivorship.[6] There is a need for an operational definitions of "optimal survivorship" that will perhaps have different elements at various stages of cancer survivorship.

Evidence-based answers to questions related to recurrence, long-term survival, effective approaches to prevent recurrence, and existential questions are simply not available. While research related to fear associated with recurrence may be helpful in terms of managing these concerns in the short run accurate data on recurrence and how to prevent actual recurrence should have a greater impact on this fear in the long run. Providers and survivors need this information. Spiritual practices also have been used to address with these concerns, however, it is important to realize that these practices whatever they be, are not consistent with the views of all survivors. This needs to be considered in future research i.e., development of approaches for those not interested in spiritual practice. Work is progressing to help answer many of the questions above, yet long-term survival is a moving target and more dynamic forms of investigation that can capture this should prove informative.

Currently, much is being made of the need for surveillance[7]. What does this really mean? Are we to simply continue to follow-up on the biology of the tumor over time or does this mean routine monitoring of many aspects of health and well-being along with tumor status?

Health surveillance is certainly a major step forward and an important one in a public health approach to cancer survivorship. This long-term monitoring needs to be comprehensive and representative of all survivors. Survivors who received care in academic medical centers do not represent the majority of the population. It is important to cast the net wide. Surveillance of a range of problems in all cancer survivors over a long period of time is critical. Also, with a focus on chronic illness and enhanced quality of life there is a need for monitoring many dimensions of "function." Global measures of function continue to be used in surveillance and this represents another limitation with most surveillance. For example, measures such as the Karnofsy Scale continue to be used by many in practice. This measure is simply too general and not very sensitive in highly functioning survivors. There are measures available to track function in those with a chronic illness and these may prove more sensitive especially in highly functioning survivors. Many current measures used in cancer survivors simply do not capture the pattern of responses and activities relevant to them (e.g., work productivity, family function, roles as parents, ability to contribute to financial status, etc.) that accurately reflect the cancer survivor of the 21st century. This needs to change.

There is also a major need for systematic research on empirically validated risk factors for fatigue, pain, cognitive limitations, relationships, general well-being, depression, stress, health behaviors, and adaptation to end of life factors that maximize optimal survivorship. Studies should be initiated using conventional epidemiological methods to begin to define a set of risk factors that we can be assured play a role in biological survival and in the many dimensions of quality of life that research to date suggests are related to "optimal survivorship." This research should be conducted for all major cancer types and the subtle and not so subtle outcomes or problems survivors' encounter. As we have seen in this handbook and the cancer survivor literature informs us that these outcomes are both negative and challenging (e.g., fatigue, and pain) and potentially positive (e.g., "benefit finding," and "renewed spiritualism"). That is, if epidemiological research indicates that commonly reported risk factors are indeed characteristic of the larger population of survivors, there is a need to truly identify these factors as casual and the variables that impact these risk factors so we can ideally prevent them from occurring in the future and also develop more effective ways of managing them. This should assist in future efforts at both primary and secondary prevention. This research should use cancer-specific outcome measures e.g., fear of recurrence,[8] more specific measurement of pain and function as well as various measures discussed in this book. It is no longer appropriate to simply use measures of psychopathology.[9]Efforts should be made to develop a wide range of measures to assess the specific concerns of cancer survivors.[8] There should also be a greater focus on functional outcomes, innovative biological markers, in addition to the use of cancer-specific self-report measures.

There is also a need to conduct studies on the mechanisms of these risk factors and how these interact with each other e.g., what is the combined role of fear of recurrence and higher levels of emotional distress or lower levels of function, if these are found to be actual risk factors. Such studies should examine the biological plausibility of these relationships and improve our understanding of psychoneuroimmunological processes that may link the psychology of the cancer survivor to the actual behavior of the tumors including the molecular biology of tumor growth and recurrence. Innovative animal and human models need to be created so that we can more aggressively understand these relationships rather than just continue to speculate as we have been for years.[9]

We also need to develop new approaches that modify risk factors over the long run once identified. Randomized Controlled Trials (RCTs) evaluating innovative primary and secondary prevention approaches for a number of critical outcomes should be a priority. Much of what the Institute of Medicine[10] and the chapters in this handbook indicate is that these efforts should be multidisciplinary and/or interdisciplinary in scope, given the complexity of many of these risk factors and potential outcomes. Providers do not need to send all these cases to all medical centers but use a team approach in their own practices. It's time to seriously consider referrals to providers that may not be on your common list when this seems justified.

The approaches that have evolved in the long-term clinics appear promising. With some creativity and persistence there is no reason why these approaches originally developed in the academic medical center cannot be expanded to primary care and the community clinic? This has occurred to some degree but needs to increase. I have been involved in multidisciplinary care since the early 1980s when developing the Pain Treatment Center and the Center for Occupational Rehabilitation at The University of Rochester Medical Center. I saw that even after many years of this approach being used for many complex medical problems there continued to be many challenges. Learning which specialists to involve, the specific roles of these specialists, team collaboration and insurance reimbursement or generation of other sources of revenue for clinical services are some of the challenges that continue to present realistic barriers. While it seems unrealistic to think such operations can be widely established outside of academic medical centers this is possible and very important public and private funding mechanisms must be mobilized. If cancer is truly becoming a widespread chronic illness on the rise in the aging population, is it too much to expect modern health care systems to act proactively and address this challenge? Also, as indicated earlier, at an individual level, by providing the type of comprehensive care discussed in this book many cancer survivors could benefit. Optimal functional restoration and well-being could then be achieved.

As many of the chapters in this book illustrate, there is a great need to focus on all stages of cancer survivorship. There is a need for greater understanding of late or advanced stages of cancer along with the need to better understand and manage the dying and grieving processes. This is an area that is very difficult to study for emotional and tactical reasons, however, a greater use of systematic qualitative and quantitative research can help move this area ahead. While this area has been primarily the province of religion, a genuine scientific understanding of the processes involved may lead to more effective ways of addressing many of the challenges related to this phase of cancer survivorship. This area is neither under the province of religion or science. Perhaps scientific study of these processes along with religious analysis can shed further light on this phase of survivorship and more importantly improve our approach to this phase of survivorship. This argument has been recently elaborated on and seems worthy of serious consideration.[11]

There is also a need for more education and training on the complexities of cancer survivorship and its optimal management. This education needs to be targeted at health care providers of all types and permeate society in general in order for true reform to occur. There is a strong need for training a new cadre of physicians, nurses, and other health care providers such as physical therapists, nutritionists, psychologists, social workers, audiologists, etc. who are well versed in the management of challenges faced by cancer survivors and stay on top of new information as it emerges. Employers need to learn about reintegration of survivors into the workplace. The public needs to be better informed as well. There is a clear need to train future researchers in the area of cancer survivorship. This should occur in many diverse settings such as community health and primary care settings along with the more common tertiary care environment. Lastly, and as importantly[12,13] we need to train survivors themselves in self-management skills so that they are better prepared to take greater control over their health care and aspects that impact the quality of their lives.[14]The use of the proposed survivorship care plan is certainly a good start. It has been recommended that the care plan include details about the cancer and its treatment, support services, contact information for providers, names and numbers of key providers, likely course of recovery, possible challenges including employment, need for ongoing health maintenance, psychosocial, financial, insurance, and genetic screening follow-up. The process of creating such a plan would go a long way toward improving knowledge and communication among providers and between providers and survivors. This coordinated effort is something that has characterized optimal care for work-injured cases for years. It continues to be a challenge because of time, personnel, and inadequate provider reimbursement to name a few barriers. This does not mean this will be the case with cancer survivors. At present an important aspect of this plan is involvement of the survivor or the cancer survivor's health navigator or partner to insure the plan covers the essential elements. Health services research can shed light on ways that can actually become part of health care in the future.

As many of the chapters in this book indicate there is a need for innovative services that are consistently offered over the long-term. These services need to be better structured to facilitate access, provide unique modes of delivery and services, and provide these services in sites other than tertiary medical centers (e.g., community-based clinics). There is also a need to work toward improving reimbursement or insurance coverage in general for many of these services. After my radiation treatment my fatigue was so extreme that I felt I needed some type of treatment to improve my energy levels. I also felt this way after chemotherapy. While medication was suggested I wanted to look into complementary medicine. My insurance would not cover any of this despite having "excellent" health insurance and a very good rationale. While I paid for the care "out of pocket"; it definitely was a factor in continuing on with the care for as long as it was actually recommended.

There is a need for better understanding and effective approaches that smoothly reintegrate the cancer survivor into society. There are many anecdotal reports and more recently epidemiological data that clearly indicate cancer survivors do experience problems reintegrating into society.[15]We need to learn more about these challenges in order to create evidence-based policies to prevent their occurrence. These challenges can and do occur for example in the workplace. More effective rehabilitation and cancer-survivor-specific accommodations should be developed and evaluated. Approaches to improve stamina, reduce fatigue, improve cognitive abilities that may have been impacted due to the treatment or the disease itself need to be developed. Theories and approaches from human factors and ergonomics may be able to assist in these efforts. There also needs to be a greater understanding

Table 1. Challenges for Cancer Survivorship: Research, Practice, Policy, and Education

Challenges	Factors
Comprehensive and representative data on the actual problems of survivors	– Patterns of occurence – How long they persist – Recurrence
More accurate case definitions of survivors	– Based on observable natural history
Long-term surveillance of cancer survivors across major dimensions of optimal survivorship both health and functional outcomes	– Multiple studies that follow survivors treated in tertiary care centers and in general practice – Routine monitoring of general health along with tumor activity – Use of more specific measures of function over time
Systematic research on empirically validated risk factors for optimal survivorship	– Operational definitions of risk factors – Research specific to major cancer types – Use of cancer-specific outcome measures and operational definitions of optimal cancer survivorship – Development of a wide range of measures to assess the many concerns of survivors – Greater focus on functional outcomes and important biological markers
Studies on the mechanisms of risk factors and how they interact with each other	– Studies of biological plausibility – Greater understanding of psychoneuroimmunology – New animal and human models
Development of new approaches that truly modify risk factors	– Determine effective interventions for a number of critical outcomes indicative of optimal survivorship
Focus on all stages of cancer survivorship	– Greater understanding of late or advanced stages of cancer – Better understanding and management of dying and grieving processes – Greater use of systematic, qualitative, and quantitative research – Scientific research along with religious analysis
Train diverse groups of health professionals	– Workshops/web-based/clinical training on survivorship management – Training in medical school and health professional schools
Long-term innovative services for cancer survivors	– Better structured services to facilitate access, provide unique modes of delivery – Better reimbursement or insurance coverage
Better understanding and effective approaches to smoothly reintegrate the cancer survivor into society	– Learn about challenges in order to create policies – Effective and cancer-survivor-specific accommodations should be developed and evaluated – Development of approaches to improve stamina, reduce fatigue, and improve cognitive abilities – Greater understanding of the risk factors for break-down or stress within the family

of the risk factors for breakdown or stress within the family and how to address these situation more effectively in terms of improving communication and loss of long-term meaningful relationships. Table 1 summarizes most of these suggestions. While many of these challenges have been posed by others, the point I would like to emphasize is yes progress has been made in many, not all of these areas, but even so it is time to increase existing efforts as well as initiate new ones.

2.0. STAGE-BASED CONCEPTUAL FRAMEWORK

Underlying future systematic attempts to improve cancer survivorship is the fundamental need for more comprehensive models or conceptualizations of factors that impact cancer survivorship over time. There are conceptualizations that have been used to guide some research in the area[9] however future efforts that integrate the many factors in the trajectory of cancer survivorship should stimulate a comprehensive understanding of factors involved.

As a relative newcomer to cancer survivorship I took the liberty to generate a conceptual framework that highlights many of the factors that I have found in my assessment of the literature, my personal experience as a cancer survivor, and my clinical work. Figure 1 illustrates some major areas that impact outcomes in cancer survivorship. The overarching point is the dynamic nature of the interactions among variables and the stages or phases of survivorship. As many of the chapters in this book indicate the variables listed in the figure can impact symptom and functional outcomes across the various stages of cancer survivorship. This conceptualization identifies six stages of phases involved in cancer survivorship: diagnosis, treatment, acute, sub-acute, chronic, and end stage. These phases of survivorship can be influenced by medical, sociocultural, individual and environmental factors. It is also possible that transitions can occur among the six stages such that an individual can move back and forth between these phases. This framework proposes that a number of variables within the four categories of variables can impact various challenges or benefits across each of the phases. Any model of cancer survivorship must await well-designed studies for validation, however, this conceptual framework can help organize research and thinking in the area. I present this as an example of a broad-based multidimensional delineation of the critical variables we need to be concerned with and how these may interact with each other to impact the several

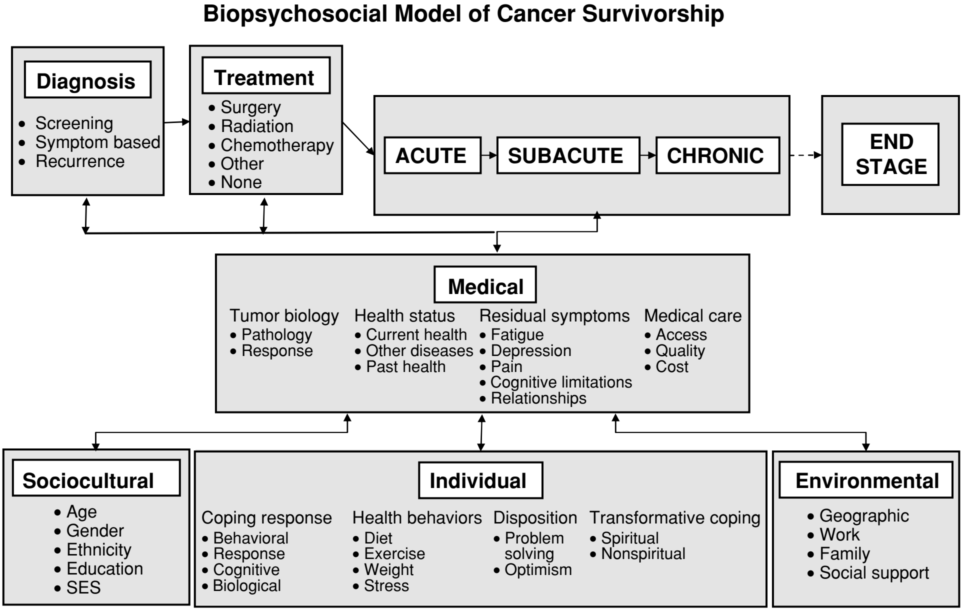

Figure 1. Example of Stage-Based Framework.

phases of cancer survivorship. Clearly, as mentioned natural history studies need to verify stages and risk factor research must identify which variables meet the criteria of a valid risk factor.

It is also important to remain cognizant of the interactive role between biological and psychological processes involved in cancer and its recovery, the reciprocal impact of functional and emotional recovery, and long-term health and quality of life. This framework highlights the dynamic interplay among multiple factors that impact the biology of cancer, the psychobiology of the person, and overall function. Lastly, with a focus on the temporal dimension of cancer survivorship in which research indicates that as the time from diagnosis, treatment, and or recurrence increases many aspects of adaptation or adjustment set in. This temporal dimension of survivorship seems important and as with many traumatic experiences several aspects of survivorship can perhaps best be considered within a temporal framework (i.e., time from some critical event- recurrence, recovery of health or functional outcome, advanced stage).

3.0. THE INSTITUTE OF MEDICINE'S PERSPECTIVE ON CANCER SURVIVORSHIP

As was discussed in Chapter 3, following a comprehensive consideration of the current state of cancer survivorship care and research the 2005, the IOM generated a report with 10 recommendations.[10] Table 2 lists these recommendations. These recommendations are based upon a careful consideration of cancer survivorship research and practice in the early part of the 21st century. The intent is that the recommendations of the committee influence future policy at national and state levels.

A few years ago I had the opportunity to be appointed to an IOM panel. It is an important and interesting exercise. The panel I was on was involved in a 2-year study of musculoskeletal disorders and the workplace. The process is balanced, comprehensive, and scientific. The goal is to generate a series of recommendations to Congress, the broad community of interested stakeholders and the general public. An important question related to this process is, " how effective is this effort in moving an agenda forward?" As we all know the answer to this question is often it depends. A "positive outcome" is often in the eye of the beholder. Who could argue with this agenda? After all, who would not want to move quality of care and quality of life among cancer survivors forward? This does, however, require the coordinated persistent efforts of many diverse stakeholders over a long period of time. Also, success is a function of just who the stakeholders are and what resources can be brought to bear on the problem. There are many stakeholders in cancer survivorship.

Stakeholders involved in this challenge are not only health care providers, researchers, and survivors but they also include employers, hospitals, health care industry, health insurance companies, those with vested interests in maintaining the status quo, those interested in change and reform, financially interested parties such as life insurance and long term care insurance companies, drug companies, and many others. There are many players and reform often is a slow process. While there is certainly a ground swell of cancer survivors and they are very successful in raising funds for research and advocacy, an important question to reflect on is, can this constituency launch a truly effective long-term public health effort where a high level of talent across many scientific and medical disciplines is needed? This will require persistence. Much more needs to be done and there is a legitimate sense of urgency.

Table 2. Institute of Medicine Recommendations

Recommendation 1

Health care providers, patient advocates, and other stakeholders should work to raise awareness of the needs of cancer survivors, establish cancer survivorship as a distinct phase of cancer care, and act to ensure the delivery of appropriate survivorship care.

Recommendation 2

Patients completing primary treatment should be provided with a comprehensiveness care summary and follow-up plan that is clearly and effectively explained. This "Survivorship Care Plan" should be written by the principal provider(s) who coordinated oncology treatment. This service should be reimbursed by third-party payers of health care.

Recommendation 3

Health care providers should use systematically developed evidence-based clinical practice guidelines, assessment tools, and screening instruments to help identify and manage late effects of cancer and its treatment. Existing guidelines should be refined and new evidence-based guidelines should be developed through public- and private-sector efforts.

Recommendation 4

Quality of survivorship care measures should be developed through public–private partnerships and quality assurance programs implemented by health systems to monitor and improve the care that all survivors receive.

Recommendation 5

The Centers for Medicare and Medicaid Services (CMS), National Cancer Institute (NCI), Agency for Healthcare Research and Quality (AHRQ), the Department of Veterans Affairs (VA), and other qualified organizations should support demonstration programs to test models of coordinated, interdisciplinary survivorship care in diverse communities and across systems of care.

Recommendation 6

Congress should support Centers for Disease Control and Prevention (CDC), other collaborating institutions, and the states in developing comprehensive cancer control plans that include consideration of survivorship care, and promoting the implantation, evaluation, and refinement of existing state cancer control plans.

Recommendation 7

The National Cancer Institute (NCI), professional associations, and voluntary organizations should expand and coordinate their efforts to provide educational opportunities to health care providers to equip them to address the health care and quality of life issues facing cancer survivors.

Recommendation 8

Employers, legal advocates, health care providers, sponsors of support services, and government agencies should act to eliminate discrimination and minimize adverse effects of cancer on employment, while supporting cancer survivors with short-term and long-term limitations in ability to work.

Recommendation 9

Federal and state policy makers should act to ensure that all cancer survivors have access to adequate and affordable health insurance. Insurers and payers of health care should recognize survivorship care as an essential part of cancer care and design benefits, payment policies, and reimbursement mechanisms to facilitate coverage for evidence-based aspects of care.

Recommendation 10

The National Cancer Institute (NCI), Centers for Disease Control and Prevention (CDC), Agency for Healthcare Research and Quality (AHRQ), Centers for Medicare and Medicaid Services (CMS), Department of Veterans Affairs (VA), private voluntary organizations such as the American Cancer Society (ACS), and private health insurers and plans should increase their support of survivorship research and expand mechanisms for its conduct. New research initiatives focused on cancer patient follow-up are urgently needed to guide effective survivorship care.

Source. Heivitt *et al.*[10] Permission granted.

4.0. THE OPPORTUNITY: REALISTIC OPTIMISM

Clearly, major funding from government and private organizations is critical but so is getting the stakeholders to the table and focusing on the right questions. If you ask three researchers or three clinicians or three employers what are the top priorities or what is the “right” approach to take they most likely will give you nine different answers. For example, one recommendation of the IOM was the use of evidence-based guidelines for cancer survivor care. While most cannot argue with this recommendation, it is easier said than done. We know that even when evidence-based guidelines are available most clinicians don’t follow them. Why? Also, in many areas of cancer survivorship at this point we don’t even have sufficient results from RCTs to create these evidence-based clinical practice guidelines.

Will response to the recommendation simply show compliance is poor or quality is poor or can we build on the knowledge of health services research in other areas of care and work on ways to operationalize the implementation of these so cancer survivors receive what they really need. Will we study ways to maximize provider adherence which should result in more survivors with positive outcomes? Does adherence to the few guidelines available at this point truly improve outcomes? Some providers do not think so. Also some employers are uncertain as well. A shift in the question for an employer might be not, “Is this going to cost me more if my employees follow these evidence-based guidelines? but rather how might following this guideline improve my employees work productivity and what is the economic value of this outcome? “While it is certainly a logical assumption that the development and use of guidelines are somehow better, we still do not know this for many clinical practice guidelines that have been generated over the past decade. The point is that we need to be realistic in our optimism, pursuit of knowledge, and quality care in this area. We need to step back and question some of our basic assumptions related to how we approach cancer survivorship so that we don’t make the same errors in health care we now know about. We need to stop and think armed with new knowledge regarding health care services and ask the right questions. We need a sense of optimism to move forward, however, we also need a sense of realism based on what we know are current challenges in the delivery of quality health care in the United States and throughout the world.

As we have read many survivors experience a pattern of societal, health care, symptom, interpersonal, and health behavior challenges. They deserve quality health care. They have been through much already. They do not need to be subjected to approaches that are ineffective, redundant, senseless, or even harmful.

5.0. WHERE IS THE SUPPORT?

A fundamental question of major significance when talking about new approaches to cancer survivorship is whether society truly views the problems of cancer survivors (i.e., the need to improve the quality of health care and quality of life) as something that is a genuine public health concern? Sure people are empathic when they hear you are a cancer survivor but is cancer survivorship really a major public health problem? Or is this just the position of a relatively few well-placed policy types, celebrity cancer survivors and the 10 million US cancer survivors, their friends, and families? There are many more than 10 million survivors when we consider the worldwide impact, yet is the base of support really strong enough to move this agenda forward? Time will tell. I hope so.

While survivors and their supporters are a large and growing group, an important question that influences the relative impact of many of the policy implications of the IOM report is, "What is the general public's perception of or appetite for the public health needs of cancer survivors?" I am sure there have been some polls but my sense as a survivor, scientist, and provider is that this is not as a major concern among the general public especially in relation to other priority public health issues such as terrorism and emerging infectious diseases. Also, a related issue is that if this is not seen as a major public health problem is it really likely that a comprehensive public health approach will be fully pursued and ultimately realized? Certainly efforts have been under way for years and that is why there has been so much done for survivors. These efforts have improved the lives of survivors, including me, and we are thankful. However an important question is, can we really expect a broad-based public health approach to successfully address this problem? Things have progressed considerably over the past 5–10 years. However, this momentum needs to be stepped up and maintained. Your efforts as health care providers and researchers are greatly needed.

6.0. THE BATTLE FOR QUALITY

The world is ready for a well-coordinated approach to cancer survivorship. Many researchers, providers, and policy makers have been working very hard to improve the lives of cancer survivors. For this we are grateful, but much more needs to be done. The chapters in this book point to challenges that remain to be solved and secondary prevention programs that need to be fully realized. It may even be possible to prevent many of these problems from occurring through effective primary prevention. Approaches to improve the quality of care and quality of life among cancer survivors worldwide need to be grounded in comprehensive well thought out descriptions of the problems, evidence as well as practical solutions to the challenges covered in this book.

The sense of urgency and effort related to cancer survivorship research and practice needs to match that of the "War Against Cancer" waged years ago.[16] Millions of battles have been fought successfully, that is why we are here, yet the war is not over. It is closer to an end than ever before. So now it is time to move certain "assets" (scientists, funds) so we can learn more about the long-term problems and improve the quality of care and lives of "veterans" of this war. It is through such an effort that we can truly realize the long-term benefits of winning the battle.

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