Michael Feuerstein
Larissa Nekhlyudov *Editors*

Handbook of Cancer Survivorship

Second Edition

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Journal of Cancer Survivorship:
Research and Practice
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Foreword

It is now more than 30 years since a small band of cancer survivors and their caregivers, along with a handful of professionals, gathered together in Albuquerque, New Mexico, to found the National Coalition for Cancer Survivorship (NCCS). We all "passed the hat" to make a small financial contribution to launch a movement to engage and empower cancer survivors, helping them to demand attention to their unmet needs related to the aftereffects of cancer treatments, including the physical, emotional, social, and spiritual consequences of life after a cancer. This grassroots effort eventually morphed into something much larger, as patient advocacy matured as an activity, and an Office of Cancer Survivorship (OCS) was established at the National Cancer Institute. All of this demonstrated the legitimacy of the concerns of cancer survivors and the pressing need for cancer survivorship research. When the OCS was established, there was only a small portfolio of research on cancer survivorship, and research has truly blossomed in the past 20 years. Further, a growing cadre of clinicians are choosing to become the health care providers for cancer survivors, and they are hungry for high-quality, evidence-based information on how to attend to the diverse needs of their patients.

Thus, it is a privilege for me to write a few words in the foreword to this second edition of the *Handbook of Cancer Survivorship* written by my colleagues Michael Feuerstein and Larissa Nekhlyudov. I have worked closely with both Michael and Larissa on various projects over the years. In fact, at about the time that Michael was publishing his first edition of the *handbook*, I was editing a "competing" book on cancer survivorship, and declined his invitation to write a chapter for his book due to lack of time. In the subsequent years, we became close professional acquaintances and ultimately edited another book together on cancer survivorship. Michael simultaneously launched the *Journal of Cancer Survivorship* that has now become the vibrant home for a large body of survivorship research, supporting the communication of the science of cancer survivorship. His contributions exemplify the amazing altruism and passion that cancer survivors so often demonstrate after having faced the realities of post-cancer treatment life, and the "new normal." Michael's contributions have been enormous, and we must all be grateful for his energy in leading the production of this second edition of the *Handbook of Cancer Survivorship.*

Larissa Nekhlyudov has added another dimension to this second edition, using her vantage as a practicing clinician caring for cancer survivors in the

context of other chronic health conditions, as well as focusing on the need for health promotion and disease prevention in everyone, including cancer survivors. She has brought new insights and chapters into this updated edition of the handbook. She knows what is needed for those in the trenches taking care of the growing numbers of cancer survivors, and this edition reflects that practical touch. Many of the new chapters focus on themes that emerged from the 2013 Institute of Medicine consensus report on *Delivering High Quality Cancer Care* [1], where Larissa so ably served. In particular, issues related to the aging of the population (and survivors) as well as the financial burdens associated with cancer care and survivorship are now included in the second edition. These new chapters help to round out the story of cancer survivorship, and point to both the opportunities and challenges in delivery of better care, as well as doing the needed research for the future.

This second edition of the *Handbook of Cancer Survivorship* is destined to become required reading for anyone involved in the care of cancer survivors. As survivorship care becomes its own discipline, there will be a need for textbooks such as this to define the clinical and research agenda. We are fortunate that Feuerstein and Nekhlyudov have brought together an outstanding group of authors in this edited volume, so that the clinical science of cancer survivorship will have a comprehensive text to build on in the future.

Los Angeles, CA, USA Patricia A. Ganz

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Acknowledgments

I am one lucky guy but not without the support of many. The first people I need to say thanks to are members of my family. My wife of 46 years has been my major source of support throughout the years. She has really stepped up after I was diagnosed and treated for my brain tumor. I am forever indebted for her never-ending understanding, support, and love. It really has made and continues to make a real difference in my life. Our children Sara, Andrew and his wife Heather Neuburger, Erica and her husband Erik Wyche, and our grandchildren Kiran, Maya, and Zain are also a major source of inspiration. I am also thankful for my younger brother David with whom I have shared a bond forever and my older brother Herbert who more recently reentered our lives.

Secondly, my colleagues all over the world in particular the United States, Canada, the United Kingdom, the Netherlands, Germany, France, Sweden, Italy, Hong Kong, Japan, and Mainland China have inspired me to keep going. Over the years our friendships and collaborations have meant so much to me. I hope these collaborations will continue for decades to come. The administration, faculty, staff, and students at the Uniformed Services University in Bethesda, MD, have provided me the opportunity to develop and expand my work on cancer survivorship and for this I am also thankful.

In addition, I want to thank all the authors of the chapters in this updated edition for all the work and thought they put into this effort. It really shows. Many thanks to Dr. Patti Ganz for writing the foreword of this edition and more importantly, for her longstanding work in the area of cancer survivorship and her support when I traversed into this unknown area as a cancer survivor committed to helping others in the same boat. The friendship and support of Dr. Julia Rowland since working with her at Georgetown University Medical Center and renewed once I was diagnosed with cancer has been unwavering. I am forever grateful.

The collaboration of the Springer editorial group over the past 30 years has provided me the opportunity to move both occupational rehabilitation and cancer survivorship along to help both injured workers and cancer survivors. All this would not be possible especially if it were not for Bill Tucker and Janice Stern (retired) at Springer. Elliot Werner was also very supportive in the very beginning when Springer was Plenum Publishing in New York.

Lastly, I would especially like to thank my co-editor Dr. Larissa Nekhlyudov. Her influence on this revision can be seen throughout the volume. Her keen focus on evidence-based clinical application has touched each

page of this book. Finally, we both would like to thank Caitlin Lupton for her excellent work in helping us pull this edition together.

Michael Feuerstein

I would like to thank Mike for inviting me to serve as co-editor of this second edition of the handbook and Patti Ganz for words of encouragement as I considered venturing into this new effort. It has been an honor and privilege to work with Mike. He has been so instrumental in advancing the field of cancer survivorship as a researcher, book and journal editor, and a survivor. He is keenly aware of the effects that his brain cancer treatment has had on his function, yet he continues to push through the challenges to do the best that he can to promote a cause he is fully committed to. It was a great learning experience for me to work with all of the authors who wrote revisions and new chapters. As I read (and reread) their chapters, I gained new knowledge about cancer survivorship, appreciating the progress made and the opportunities remaining.

I would like to thank my husband Peter Meyer who has consistently supported my career, from my premedical studies through the present. He has at times questioned the hours that I spend on my academic travails (and at times made me do the same). Such conversations often led me to shift my focus into directions that ended up being more professionally and personally meaningful. My mother-in-law Alice Yaker (a two-time breast cancer survivor) has also been an important role model and partner. We have shared many in-depth conversations that have shaped my understanding about the impact of my work on the day-to-day lives of cancer survivors. Thank you to my sons, Jonah and Andrew, for dealing with my travel schedule, even when gifts do not accompany my return. Professionally, I thank my many national and international colleagues who have taught and inspired me over the past two decades. I am so grateful to have had the opportunities to work and learn from so many tremendous mentors and colleagues.

Larissa Nekhlyudov

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Part I

Overview of Cancer Survivorship

1 Cancer Survivorship: A Bird's Eye View from an Insider a Decade Later

Michael Feuerstein

1.1 The Need for a Revised Handbook

It has been a little over a decade since the first edition of the Handbook of Cancer Survivorship was published. The numbers of cancer survivors continue to increase and given aging trends there is every reason to assume the number will rise to higher levels. This is great news for the millions of individuals newly diagnosed and treated for this often dreaded illness and for their loved ones. Yet, certain individuals who make it through the maze of detection, treatment and management face a set of challenges for years to come. Even decades after having survived diagnosis and treatment and the many advancements over the years, these long – term survivors are still often left to fend for themselves.

Challenges for many cancer survivors continue despite an increased awareness and improved reporting of these problem areas [1]. There is a greater awareness of the various problems related to health and well-being among cancer survivors. There is also a greater emphasis being placed on preserving residual function following treatment protocols for many types of cancers, allowing patients an opportunity to function in many of the roles they held prior to their cancer diagnosis and treatment. Despite these positive trends, problems persist and opportunities for improvement abound.

The chapters in this Handbook provide up to date coverage of the progress made and the challenges that remain. This volume covers the science of cancer survivorship from concept to clinical practice, and provides emerging evidence that serves as a foundation for future efforts. The increased emphasis on ways to help cancer survivors become actively engaged in self-care efforts is also covered.

It is critical that we continue to improve how we manage the concerns of the individual cancer survivor taking into account unique patterns of health and treatment history. These individuals can present with persistent pain, recurrent bouts of fatigue, working memory deficits, clinical and sub-clinical levels of depression, marital and sexual problems, emerging health risks such as metabolic disease or other co-morbidities, premature aging, late effects of treatment and new or recurrent cancers. It is well recognized that these challenges need to be addressed following primary treatment for cancer and over the long- term. Providers who care for these patients (whether oncology, primary care, other physician or non-physician providers) need to keep their "eye on the ball" in order to prevent or detect these

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potential problems if they occur. As new approaches for managing survivorship- related problems has emerged, access to these interventions must be improved. It is not just enough to know that these approaches exist; we must work toward offering these options in an accessible and affordable manor.

1.2 My Story

In June of 2002, at 52 years of age, after a lifetime of excellent health, as most know by now, I found myself thrust into the quagmire of "cancer survivorship". After crossing a busy street in Washington, D.C. in midday traffic in what seemed like a drunken stupor or stroke, an MRI and brain biopsy indicated that I had an anaplastic astrocytoma grade III in my right cerebellum spreading to my pons; an inoperable tumor of the glial cells of the brain. They now tell me I'm one of the lucky ones, the few on the far right of the survival curve. Yes, after 15 years I am still around. On a positive note, I have been able to participate in major family and career milestones. I probably have harnessed the neuroplasticity available to us all as we persist despite challenges including long term and late effects of treatment such as: fatigue, depression, vision and hearing impairment and memory deficits.

From a negative perspective, despite my persistent efforts, I found it difficult to remember intellectual conversations while teaching graduate level seminars. I found these limitations frustrating. My difficulties rapidly "encoding" conversations led to a slowing of information processing that made teaching in a fast paced environment particularly challenging. Despite tenure at the university that I had worked at for 24 years, I left my academic position as Professor. Sure some may say, "Oh well not much of a price to pay", but I did love my work and I planned on working at least three more years. There have also been many challenges for my loved ones as I have become more forgetful, experience less desire to interact with others, increasing problems hearing and communication skills that are not as fluid as they once were in the past. I guess there are biological limits to full recovery regardless of my efforts.

During my experience as a survivor, I have seen the development of new information in the areas of epidemiology, symptom assessment and control, functional restoration, and the provision of quality patient information. I have also experienced first-hand, innovations in health care provided to cancer survivors and observed greater reengagement in social roles (e.g., employee) played by cancer survivors. Despite this progress, many of these advances now require greater levels of integration into every day health care, improved access for those who can best benefit from them and further development of evidence-based approaches effective in achieving desired longer term outcomes. Over the past decade I have also had the good fortune to observe how advocates develop policy and work tirelessly to improve approaches to both medical and non-medical problems in areas of detection and management.

It has also become clear to me that despite an interest in caring for the many challenges of cancer survivors, for the most part oncologists remain rightly focused on keeping patients alive. Some remain connected to the patient who has survived over time and manage problems that crop up; however, new patients take priority. This ever-growing group of patients referred to, as cancer survivors, clearly will require innovations in current practice. There is a growing number of internists, other physicians, non physician specialties including nurses who are now more capable and interested in managing many problems that can occur following primary treatment for cancer. There is a critical need to expand such expertise and increase access to them.

1.3 The Synergy of a Co-Editor

The addition of co-editor Larissa Nekhlyudov, MD, MPH, an internist with expertise in cancer survivorship, has added this new perspective to this 2nd edition of the Handbook. It is hoped that

the dissemination of the new knowledge reported in this revision is more readily taken up by mainstream health care. Dr. Nekhlyudov has been actively involved in the reorganization, bringing in new content, and editing all chapters in the current revision of this book to increase its relevance to many types of clinicians, both in oncology and primary care. Her extensive clinical, policy and research experience provides the perspective of an experienced internist to help translate the information in this volume into daily practice.

1.4 Content of this Edition

Aside from the inclusion of a co-editor, this book is more than simply a revision of the original publication. Specifically, the second edition of the Handbook is now organized into seven major topic areas with a total of 21 chapters. The first broad topic area provides the reader with a foundation of cancer survivorship including new chapters on the epidemiology of cancer survivorship, what is currently viewed as quality health care for cancer survivors and more specific coverage of the processes involved in coping with or adapting to a cancer diagnosis and treatment.

Another important area that cancer survivorship research and practice focuses on is the area of health disparities. This topic is covered in greater depth in the current version of the handbook. It remains widely acknowledged that not all cancer survivors represented in society experience equal health care access, quality care or similar outcomes. Despite the data that indicate the majority of cancer survivors are over 65 years old, it has only been recently that age specific cancer survivorship care has become a reality for many. The chapter on aging covers this emerging area and provides guidance for quality health care in this group. The final chapter in this section focuses on the major financial burdens that can be experienced by cancer survivors and provides a perspective on costs and the potential economic impact of living after cancer.

The next two sections of this edition include chapters related to potential long-term or late effects of diagnosis and or treatment. The problems included in these chapters cover symptoms such as fatigue, distress and pain and changes in function including cognition, work status, sleep and interactions with others both within and outside the family. It is important that readers recognize that not all individuals diagnosed with and treated for various cancers experience all or any of these problems.

The next section of chapters addresses certain lifestyle behaviors that can also impact the long-term health and well-being of cancer survivors. It is important to keep in mind that as with most chronic illnesses, lifestyle (specifically, physical activity, nutrition, weight management and smoking) is a major aspect of providing quality care to cancer survivors.

Over the past decade several approaches have emerged to help optimize health care delivery for cancer survivors. A new chapter describing cancer survivorship care models that have emerged over the last decade has been included. There is also a new chapter that provides the rationale and describes an approach that supports the role of primary care in cancer survivorship health care as another potential solution to this growing population of patients.

While these approaches to cancer survivorship care are being implemented in many countries, they are not available in others. The chapter on international efforts related to cancer survivorship is not intended to cover the globe. However, it does provide a comprehensive review of activities related to cancer survivorship in certain countries and provides examples of the emerging global network that has evolved for the most part over the last decade. In the final chapter of this version of the Handbook, Dr. Nekhlyudov and I highlight the progress made and the questions remaining. We hope that the next decade will bring us closer to answering those questions.

This Handbook does not address childhood or young adult cancer survivors and the unique challenges experienced by these individuals. Suffice it to say that these individuals are not and should not be considered or treated as simply "younger versions of adult cancer survivors".

We refer the readers to recent publications focusing on adolescent, young adult cancer survivors and survivors of childhood cancers [2].

1.5 The Authors

I want to take this opportunity to thank all those who contributed to both the first and second editions of this book. In the second edition we integrated certain chapters from the first edition, and added new chapters to cover certain topics in greater depth or areas that have emerged or significantly evolved since the first edition.

This revised edition of the Handbook of Cancer Survivorship provides a timely update while also addressing new topics designed to facilitate quality integrated cancer survivorship care. The chapters in the book provide timely overviews of both current knowledge and gaps in our understanding and management of common problem areas observed among cancer survivors.

1.6 Conclusion

Despite the progress reported in this second edition of the Handbook of Cancer Survivorship, we are reminded that knowledge and its application to improve outcomes in cancer survivorship are far from complete. Yes, cancer survivors are living longer and many are grateful for the opportunity to do so, but for some…at what cost, especially over time? Efforts to better understand how to prevent or effectively mitigate the many potential iatrogenic effects of cancer diagnosis and treatment along with the challenges cancer survivors confront throughout their lives must continue in both research and ongoing care.

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Epidemiology

2

Julia H. Rowland, Angela B. Mariotto, and Joanne W. Elena

2.1 Introduction

There is probably no more dramatic or compelling evidence of the progress made in identifying, curing, and managing the many diseases referred to as "cancer" than the rising number of those alive today with a history of cancer. At the same time this population, now living years or decades beyond an original diagnosis, presents a unique challenge to society at large and the healthcare delivery system in particular. Few, if any, of the modern cancer therapies are entirely benign. Many survivors—and their families— struggle with the persistent or late occurring effects of curative therapy. Determining how best to continue to care for and support these individuals is one of the great challenges for health care in the twenty-first century. In this chapter, we will provide a brief history of the epidemiology of survivors in the United States (U.S.) population, describe the current prevalent population, highlight some of the methods used for following survivors and some findings from this work, and provide insights for the future of cancer survivorship epidemiology.

Note. All tables and figures are in the public domain. US Government.

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2.2 Historical Perspective: The Rise of Survivors and the Science of Survivorship

When President Nixon signed the National Cancer Act in December 1971, and declared what would soon be called 'the war on cancer,' fewer than half of those diagnosed with cancer could expect to be alive in 5 years (the estimates for Whites was 43% and for Blacks 31%). Treatment options for most cancers were limited and many involved aggressive therapies with limited efficacy, delivered largely in hospital settings, and whose side effects were poorly controlled [1]. Available cancer-directed psychosocial and behavioral interventions, to the extent that these existed, were geared toward helping those diagnosed cope with or die of their disease, not live well with or beyond it. Arguably, the 'cancer survivors' in this earlier period were more often the family caregivers than patients themselves [2].

In the past four decades, a number of advances served to fundamentally change the landscape of cancer survivorship in the U.S. These included improvements in screening and early cancer

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detection and in the efficacy of cancer treatments and their delivery, along with broader application of targeted supportive care enabling patients to be better prepared for and to better tolerate and recover from treatments received [3].

The structure of how cancer care was delivered also changed. In 2018, the majority of cancer patients have multiple treatment options, typically undergo multimodal therapy (with a combination of surgery, radiotherapy, chemotherapy, hormonal therapy, immunotherapy, and/or biologic treatments), delivered predominantly in out-patient settings or even at home, and will live years beyond their diagnosis [4, 5]. Patients are better informed through the advent of social media and often work with their providers to tailor their treatment experience to include changes in diet, physical activity, and a focus on the mind -body connection [6–9].

As directed by the National Cancer Act, in 1971, the National Cancer Institute created the Surveillance, Epidemiology and End Results or SEER tumor registry system to help track progress made in national efforts to promote cancer control (www.cancer.gov/about-nci/legislative/history/national-cancer-act-1971). The Act made cancer a reportable disease. Data from SEER registries permit examination over time of rates of cancer incidence, mortality and survival, and more specifically prevalence, the number of people living with a history of cancer across the country. Because the registries were only created in 1973 (and were limited in geographic coverage) early prevalence statistics were limited to 5-year outcomes for reporting purposes. One exception to this was the Connecticut tumor registry. Because it was established in 1935, information on those who may have been diagnosed in earlier years could be captured, enabling estimates on what is referred to as complete (versus limited duration, e.g. 5-year survival) prevalence. Based on the Connecticut registry data and backwards projections from the SEER-9 registries, it was estimated that there were only 3 million cancer survivors in the U.S. in 1971 [10]. As the number of those surviving treatment grew over the following decades, so too did attention to their unmet and poorly understood needs.

In 1986 a group of two dozen individuals comprised of those who had lived through cancer treatment, cancer care providers and/or represented cancer support program leaders gathered in Albuquerque, New Mexico and created the National Coalition for Cancer Survivorship (NCCS) (https://www.canceradvocacy.org/). One of the first tasks they undertook was to redefine what it meant to be a survivor. At that time, the medical definition of a cancer survivor was someone who had remained disease free for 5 years. By 1986, however, more than 50% of those diagnosed could expect to live this long [11]. NCCS founders argued that an individual could not put his or her life on hold and simply wait to see if he or she would make it to 5 years. They felt it was critical that thought be given to long-term well being from the outset. In an effort to change the dialogue, they embraced the concept that an individual could call him- or herself a cancer survivor from the moment of diagnosis and for the balance of that person's life (see Box 2.1).

Box 2.1 Definitions

Cancer Survivor

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.

Adapted from the National Coalition for Cancer Survivorship

Cancer Survivorship Research

Cancer survivorship research encompasses the physical, psychosocial, and economic sequelae of cancer diagnosis and its treatment among both pediatric and adult survivors of cancer. It also includes within its domain, issues related to health care delivery, access, and follow up care, as they relate to survivors. Survivorship research focuses on the health and life of a person

(continued)

Box 2.1 (continued)

with a history of cancer beyond the acute diagnosis and treatment phase. It seeks to both prevent and control adverse cancer diagnosis and treatment-related outcomes such as late effects of treatment, second cancers, and poor quality of life, to provide a knowledge base regarding optimal follow-up care and surveillance of cancers, and to optimize health after cancer treatment.

Source: Office of Cancer Survivorship, National Cancer Institute

It is important to note that this definition remains controversial. Many individuals diagnosed with cancer do not think of themselves as a survivor at any point in time [12]. Some adamantly reject this reference. While still others think of themselves as thriving post-cancer, not merely surviving [13, 14]. Nor is the term widely used or accepted in many countries outside the U.S. [15]. The definition was not intended to become a label. What the Coalition members did intend was to provide a message of hope, that there was good life to be had after cancer; and to ensure that conversations occurred between patients and their oncology providers *prior* to treatment onset about what was important to these survivors as an outcome, their individual preferences and goals for treatment. They also sought to eliminate the use of the term 'victim' – and its connotation of being helpless and hopeless in the face of illness – as a reference for anyone who had cancer.

In addition to redefining what it meant to be a cancer survivor, NCCS founders promoted the concept that the cancer experience itself had distinct periods. These included the acute phase, encompassing the active treatment period, and the post-treatment phase, which is further, subdivided into short-term (2–5 years post-treatment, equivalent to Mullan's "extended survival") and long-term (5 or more years post-treatment, or "permanent survival") [16]. The view that cancer has unique trajectories has been more broadly embraced [15, 17].

In anticipation of their first national congress on cancer survivorship held in Washington, D.C., in November 1995, NCCS surveyed nationally recognized individuals with expertise in the areas of quality cancer care, physiologic effects of cancer treatment, and psychosocial issues. Based on the information collected they generated position papers in these three topic areas. After further refinement solicited at the congress, NCCS published these under the title, *Imperatives for Quality Cancer Care: Access, Advocacy, Action, and Accountability*, a document that represented the first national cancer survivorship report and recommendations for action [18]. The report led to the establishment of the Office of Cancer Survivorship (OCS) at the National Cancer Institute in 1996.

Research on the long-term and late occurring effects of cancer has grown rapidly in the more than two decades since the NCI made this investment in supporting survivorship science (see definition of survivorship science in Box 2.1). This is reflected in the steady rise in both the number of grants and level of funding for survivorship research at the NCI (https://cancercontrol.cancer.gov/ocs/funding/index.html). It is also manifest in the now half-dozen national reports focusing on this aspect of survivors' care [19–24]. Two important findings are highlighted in all of these documents. First, as articulated by the advocacy community, survivorship represents a distinct place on the cancer control trajectory. Second, cancer has the ability to affect every aspect of an individual's life: physical, psychological, social, economic and existential. As addressed in a number of chapters in the present volume, assessing risk for and preventing when possible, or mitigating when not, diverse long-term and late-occurring effects of cancer is critical to improving the health-related function and well-being of the growing population of cancer survivors. Key to success in efforts to do this includes understanding the demographics of current survivors, anticipating those of future cancer survivors, and finding ways to track our progress in improving not simply the lifespan, but more importantly the *health span* of all survivors.

2.3 The Changing Profile of Cancer Survivors/ Survivorship

Cancer survivors represent a growing population, heterogeneous in their cancer trajectories and need for medical care. In the U.S., data from the SEER cancer registries (collected across eight states: CT, HI, IO, KY, LA, NJ, NM, UT and seven regional registries: Atlanta, Detroit, Los Angeles, Northern California, San Francisco-Oakland, San Jose-Monterey, Seattle-Puget Sound) is the primary source of information to track and report the evolving profiles of cancer survivors. The initial SEER-9 registries (CT, HI, IO, NM UT, Atlanta, Detroit, San Francisco-Oakland, San Jose-Monterey, Seattle-Puget Sound) are used to estimate complete prevalence. The SEER registries collect quality-controlled information on demographics, disease characteristics at the time of diagnosis, and aspects of initial therapy, for a complete census of newly diagnosed patients in the registry catchment areas. Collectively, SEER registries cover approximately 30% of the U.S. population. Annual linkages with mortality and administrative databases provide information on vital status. The verified information at diagnosis, the complete enumeration of cancer cases in designated areas and survival makes cancer registries the ideal source of data for calculating prevalence estimates.

Cancer prevalence estimates and projections using data from SEER registries have been extensively used to quantify the burden of cancer [25, 26] inform survivorship research [27–30] and guide health services planning and allocation [31, 32]. This section describes the prevalent population of cancer survivors, defined here and throughout this section as all those alive at a given point of time with a cancer history, and provides estimated projections by different demographic characteristics and trajectories. Multiple methods and different aggregations of SEER registries are used to provide a bird's eye view of cancer survivorship in the U.S.

2.3.1 Projections of Cancer Survivors and Aging

As previously reported [4, 33–35], the number of cancer survivors is continuously increasing and aging. In 2018, we estimate there are 16.5 million cancer survivors (Fig. 2.1) among whom survivors of female breast cancer (3.8 million), prostate cancer (3.5 million), colorectal cancer (1.5 million) and melanoma (1.3 million) constitute the largest disease groups; combined these survivors represent 62% of the prevalent population (Table 2.1). The majority (63%) of cancer survivors in 2018 are age 65 or older. Sites with the largest number of older survivors (≥65 years) are prostate (81%), bladder (80%), lung (76%) and colorectal cancer (75%) (Table 2.1).

The number of cancer survivors in the U.S. has been steadily increasing since 1975 (34) (Fig. 2.1). This historical trend, from 1975 through 2012 (the last year for which data are available), is largely attributable to the aging of U.S. population, with some contribution due to the increase in incidence rates until 1992 for men and between 1979 and 1987 for females [3], as well as improvements in cancer survival [3]. The number of U.S. cancer survivors is projected to reach 21.2 million in 2028 and 26.1 million in 2040 (Fig. 2.1). As cancer survival and incidence trends from 2013 through 2040 are assumed constant, these projections reflect the impact of the aging of baby boomers and increase in life expectancy, as well as the absolute increase in the numbers of the U.S. population from 2013 to 2040.

It is estimated that by 2028, 71% of all survivors will be age 65 years or older. The highest rate of increase in the number of cancer survivors, with approximately 0.5 million survivors added each year, is expected to occur between 2018 and 2030. After 2030 the increase will begin to slow down. The growth of the cancer survivor population will put pressure on the healthcare system as their numbers may outpace cancer drug supplies, and are already anticipated to overwhelm available provider systems from oncologists [36, 37], to primary care clinicians

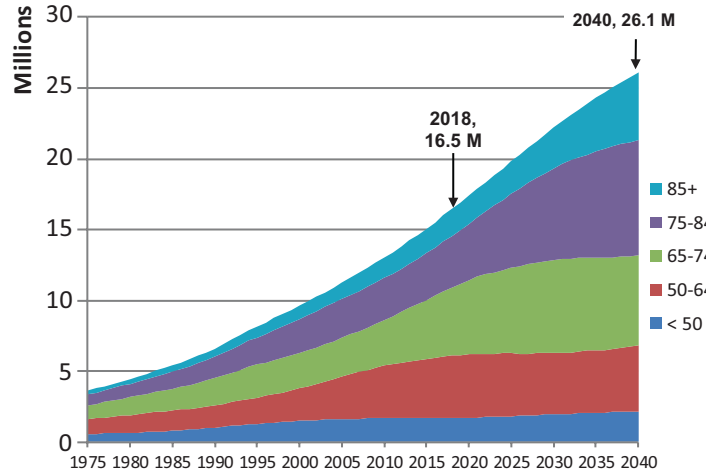

Fig. 2.1 Estimated and projected numbers of US cancer survivors by age at prevalence. Projections after 2013 are based on the US census population projections and flat cancer incidence and survival trends [34]

Table 2.1 Projected number of cancer survivors at 1/1/2018 by cancer sites, sex and age (all ages and 65 and over). Percent representation by site of cancer survivors 65 years and older

	Prevalence counts (all ages)			Prevalence counts (65 years and older)			%65 years and older
	Male and female	Male	Female	Male and female	Male	Female	Male and female
All sites	16,451,843	7,881,281	8,570,562	10,380,614	5,317,200	5,063,414	63%
Bladder	807,898	607,385	200,513	649,584	488,609	160,975	80%
Breast	3,760,575	–	3,760,575	2,368,710	–	2,368,710	63%
Cervix	282,923	–	282,923	135,560	–	135,560	48%
Colorectal	1,512,995	758,630	754,365	1,134,361	555,655	578,706	75%
Oral Cavity	370,554	242,835	127,719	215,965	138,692	77,273	58%
Kidney	549,334	329,727	219,607	337,532	202,580	134,952	61%
Leukemia	436,979	248,107	188,872	212,709	121,838	90,871	49%
Lung	556,387	251,556	304,831	420,379	190,425	229,954	76%
Melanoma	1,313,337	661,054	652,283	692,741	388,735	304,006	53%
Ovary	244,567	–	244,567	136,676	–	136,676	56%
Prostate	3,532,954	3,532,954	–	2,861,787	2,861,787	–	81%
Corpus	790,363	–	790,363	559,092	–	559,092	71%
Hodgkin	229,793	117,886	111,907	48,057	25,391	22,666	21%
NHL	733,836	387,195	346,641	440,168	221,113	219,055	60%
Thyroid	868,647	188,672	679,975	314,893	78,660	236,233	36%
Testis	280,735	280,735	–	49,723	49,723	–	18%

[38] to nurses [39]. This in turn will have significant implications for the economic burden of cancer [4, 34]. The growing number of older survivors also presents a unique challenge to the healthcare system as they are more likely to have multiple chronic diseases and tend to experience poorer physical functioning both pre- and post-cancer than younger survivors, [40–42] making treatment choices more difficult and care delivery more complex.

2.3.2 Ethnocultural Diversity

In addition to the impact of an aging nation, growing ethnocultural diversity across the population will affect cancer prevalence trends as well [43]. To estimate prevalence by race and ethnicity we used an expanded set of registries (SEER-13 excluding Alaska), which have reported incidence cases from 1992 and represent 14% of the U.S. population. These data allow for more

Table 2.2 Number of US cancer survivors 0 to 22 years from diagnosis of major cancer sites and US male and female population at 1/1/2014 by race and ethnicity

	All races	White	Black	API	Hispanic
No. of US cancer survivors in Millions					
All sites	13.36	11.47	1.24	0.39	0.87
Breast	3.00	2.59	0.27	0.11	0.18
Colorectal	1.21	1.01	0.13	0.05	0.08
Prostate	3.05	2.52	0.40	0.06	0.16
US population in millions					
Males	156.33	123.77	21.10	9.21	27.72
Females	161.34	126.15	22.94	10.02	27.08

accurate estimates of prevalence by race/ethnicity. All reported prevalence estimates are 22-year limited duration prevalence representing cancer survivors alive at 1/1/2014 and diagnosed between 1/1/1992 and 12/31/2013.

In general, the race/ethnicity make-up of cancer survivors mimics that of the U.S. population. The majority of survivors are white (11.5 million), followed by blacks (1.2 million), Hispanics (0.9 million) and Asian and Pacific Islanders (API) (0.4 million) (Table 2.2). However, the prevalence of cancer survivors within each race/ethnicity population varies. The prevalence of breast cancer survivors among whites is the highest, followed by blacks, API and Hispanics (Figure 2.2a). Among women aged 75–79 years the percent of breast cancer survivors is 7.5%, 5.7%, 4.4% and 4.4% among whites, blacks, API and Hispanics, respectively. This ranking reflects the fact that whites have both the highest breast cancer incidence rates as well as the highest survival. Although API women have the highest breast cancer survival, they have low breast cancer incidence [3, 5].

Blacks have the highest prevalence of prostate cancer; 21.6% of black men aged 75–79 years had a prostate cancer diagnosis in the last 22 years versus 15.0%, 11.8%, and 7.4% among white, Hispanic and API men respectively of the same ages (Figure 2.2b). The high prevalence of prostate cancer among blacks is reflective of their high incidence rate, a figure that is almost double that for whites: 205.3 versus 118.0 age-adjusted incidence rates per 100,000 population among blacks and whites, respectively [3, 5]. There is less variability in the prevalence of colorectal cancer among the race/ethnicity groups compared to breast and prostate cancers. The prevalence of colorectal cancer is slightly higher among blacks up to age 84 years and higher among whites aged 85 years or older (Figure 2.2c).

2.3.3 Cancer Survivorship Trajectories

SEER prevalence data provides estimates about the number of individuals who are currently alive following a cancer diagnosis. However, its ability to provide information regarding survivors' health status or phase of cancer trajectory is more limited, e.g. how many individuals are in the acute phase of survivorship from diagnosis to the end of initial treatment, are long-term survivors who have been cured of cancer, or those who have advanced or chronic cancer requiring ongoing cancer therapy, represent individuals who are post-treatment but experiencing one or more serious, late complications of treatment, may be individuals who developed a second cancer, or represent individuals whose cancer has recurred. Capturing cancer recurrence is particularly difficult and represents a significant challenge to efforts to better delineate survivorship trajectories [44, 45]. Prevalence by time since diagnosis nevertheless can offer a general proxy for survivorship by phase in the cancer trajectory. Specifically, we can identify survivors receiving more intensive care in the first year after diagnosis (0–1 years from diagnosis), survivors in a

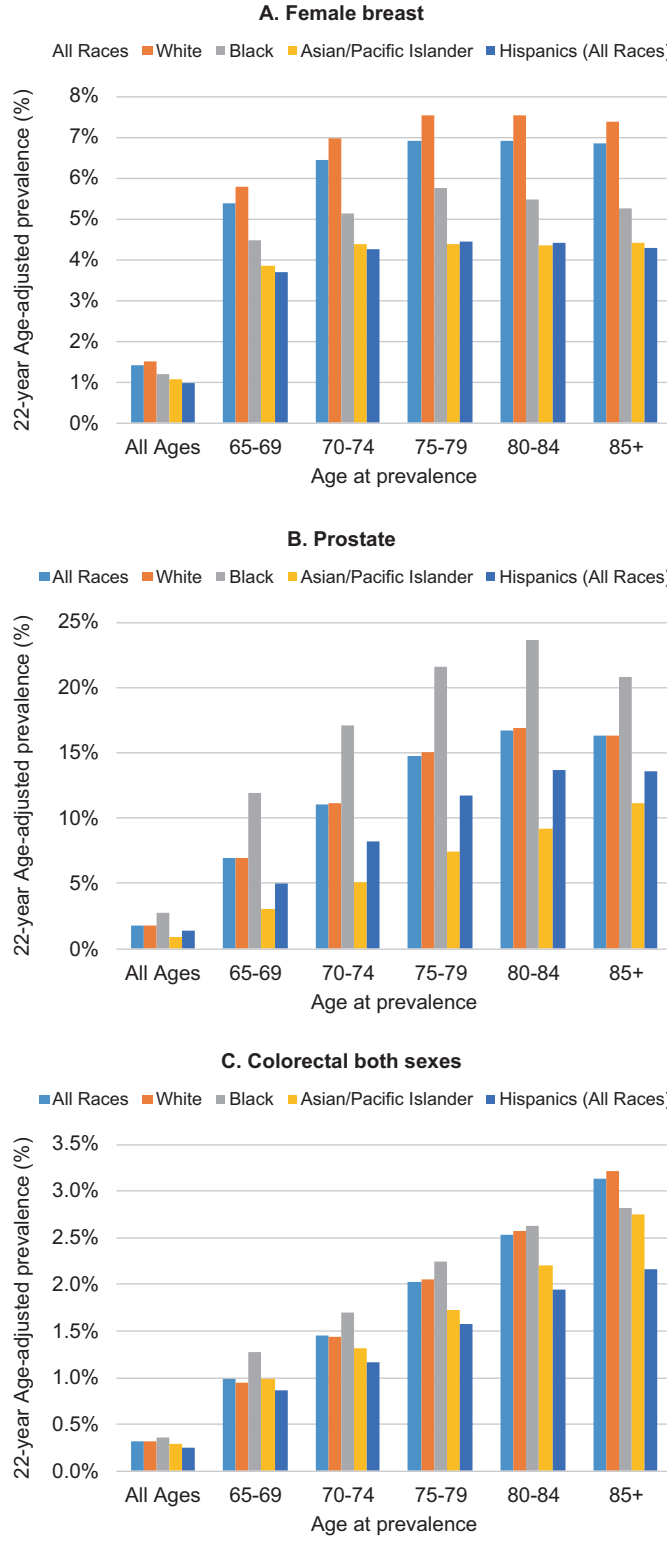

Fig. 2.2 Percent of (A) breast, (B) prostate and (C) colorectal cancer survivors diagnosed between 1/1/1992 and 12/31/2013 among each respective sex/race/ethnicity population by age. The 22-year percent prevalence is calculated at 1/1/2014 and age-adjusted to the US 2000 standard population. The table shows the estimates 22-year prevalence counts at 1/1/2014 by race and ethnicity. Source: SEER 13 excluding Alaska

more intensive monitoring phase (1–5 years from diagnosis), and long-term survivors (5 or more years from diagnosis).

Using this approach, it is estimated that 5.4 million, 3.7 million and 7.3 million have survived 0–5 years, 5–10 years and more than 10 years, respectively, representing 33%, 23% and 45% of the 16.5 million cancer survivors in 2018. Although the proportion of long term survivors is quite high overall, there is considerable heterogeneity in the proportion of long-term survivors by cancer site (Fig. 2.3). For example, cervical cancer survivors have the highest proportion of survivors living 10 or more years from diagnosis (70%). By contrast, among lung cancer survivors only 20% have survived ≥10 years or more after diagnosis. In general, the proportion of long-term survivors for a given cancer is both a function of the 5-year survival rates for that cancer as well as the median age at diagnosis. The proportion of long term survivors is likely to be higher for cancers with a high 5-year survival rate and younger median age at diagnosis (Tables 2.3 and 2.4). Older adults not only have shorter expected lifespans than younger adults, they typically have other competing comorbid conditions that may cut short their length of survival following a cancer diagnosis [34].

2.3.4 Prevalence of Multiple Tumors

Estimates indicate that of the approximately 14.4 million survivors diagnosed between 1975 and 2013, 1,599,751 are people living with a history of multiple primary cancers, representing 11% of survivors (Table 2.5). Of these individuals, 1,249,293 (78%) had two or more cancers of different primary sites, whereas 350,458 (22%) were diagnosed with two or more tumors of the same site. After adjusting to the 2000 U.S. standard population, the observed differences in cancer prevalence among white and black males disappear but black women have a lower prevalence compared to white women.

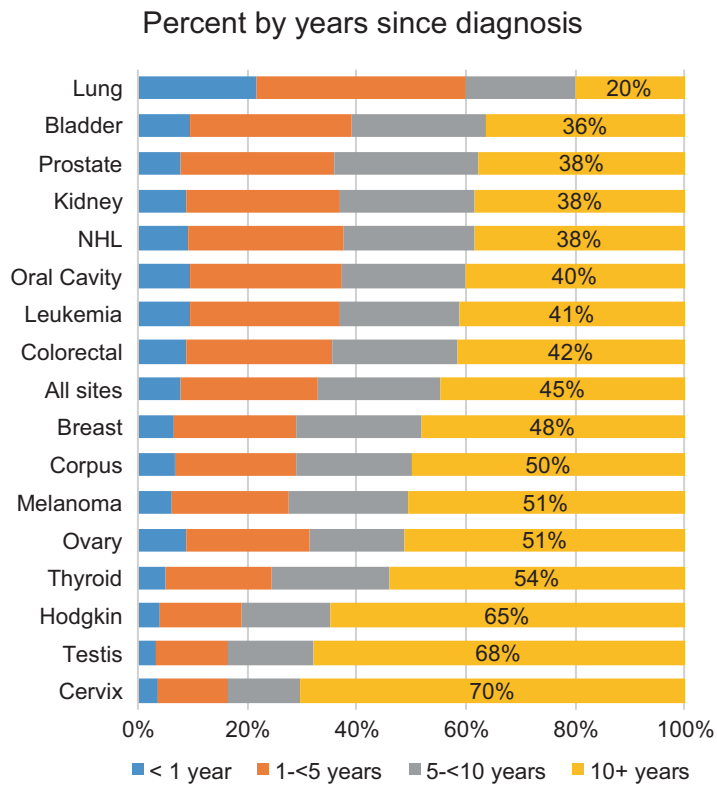

Fig. 2.3 Estimated number of cancer survivors in the United States as of January 1, 2018 by cancer site and years from diagnosis. Cancer sites by ordered proportion of survivors 10+ years from diagnosis. Median age at diagnosis for patients diagnosed in 2010–2014 and 5-year relative survival for patients diagnosed with cancer in 2007–2013 in the SEER-13 areas

Table 2.3 Median age at diagnosis for patients diagnosed

Site	Median age at diagnosis
Cervix uteri	49
Testis	33
Hodgkin lymphoma	39
Thyroid	51
Ovary(b)	63
Melanoma of the skin	64
Corpus uteri	62
Breast	62
Colon & Rectum:	67
All sites	66
Leukemia:	66
Oral Cavity & Pharynx:	63
Non-Hodgkin lymphoma	67
Kidney & renal pelvis	64
Prostate	66
Urinary bladder	73
Lung & bronchus	70

Table 2.4 5-year relative survival and 95% confidence intervals for people diagnose in SEER-18 areas between 2007 and 2013

Cancer site	5-year relative survival	95% Confidence interval
Cervix uteri	67.1%	(66.4%, 67.9%)
Testis	95.1%	(94.6%, 95.5%)
Hodgkin lymphoma	86.4%	(85.7%, 87.1%)
Thyroid	98.2%	(97.9%, 98.4%)
Ovary	46.5%	(45.9%, 47.2%)
Melanoma of the skin	91.7%	(91.4%, 92.0%)
Corpus and uterus, NOS	81.3%	(80.9%, 81.7%)
Breast (female)	89.7%	(89.5%, 89.9%)
Colon and Rectum	64.9%	(64.6%, 65.1%)
All cancer sites	67.0%	(66.9%, 67.0%)
Leukemia	60.6%	(60.1%, 61.1%)
Oral cavity and pharynx	64.5%	(64.0%, 65.0%)
Non-Hodgkin lymphoma	71.0%	(70.6%, 71.3%)
Kidney	74.1%	(73.7%, 74.6%)
Prostate	98.6%	(98.5%, 98.8%)
Urinary bladder	77.3%	(76.8%, 77.7%)
Lung and bronchus	18.1%	(17.9%, 18.3%)

The number of survivors with multiple tumors doubled from 756,467 in 2002 [29] to 1,599,751 at January 1, 2014. This is a function of cancer survivors living longer, as well as the larger number of older cancer survivors secondary to the aging of the U.S. population. Research among survivors of multiple cancers continues to be sparse. However, in their review of the literature, Belcher and colleagues found that when compared with single cancer survivors, those experiencing multiple primary cancers had lower global quality of life (d = 0.32–0.37), poorer emotional role function and stress (d = 0.08–0.20), greater and more frequent distress (d = 0.11–0.37), and greater subclinical anxiety (d = 0.15). While depressive symptoms were variable (d = 0.01–0.22), no differences between MPC and single cancer groups were identified for sleep and suicidal ideation [46].

2.4 Platforms for Survivorship Epidemiology and Some Key Findings

While data on cancer prevalence relies heavily on cancer registries, our understanding of the etiology and management of cancer survivorship outcomes comes from a range of sources. There are many different study designs that are routinely used to study the factors affecting the quality of life and function of cancer survivors. These include, but are not limited to: clinical trials, national health surveys, longitudinal cohort studies, electronic medical records from provider networks, registry-based studies, and cross-sectional studies.

Different research questions may require different approaches, with the optimal choice of research design and platform determined by a combination of the type of information queried, the quality of the information collected, the study population of interest, timing of measurements and ultimately, what is feasible based on available resources. There are notable caveats when studying survivorship including reverse causation, confounding, and information bias. Fortunately, there are specific steps that can be taken to minimize these biases through appropriate study design and in the analytic approach [47,

Table 2.5 Prevalence of people alive at January 1, 2014 who had at least one malignant tumor in the last 39 years, by number of malignant tumors. Prevalence estimated from SEER-9 data

US prevalence counts (number of people)							
		All races both sexes					
		Multiple malignancies		White		Black	
# tumors	Total	All same site	Different sites	Male	Female	Male	Female
1	12,817,599	n.a.	n.a.	5,310,138	5,872,970	601,712	576,047
2	1,400,513	331,121	1,069,391	558,487	693,093	51,596	58,990
3	171,059	17,287	153,772	71,133	83,637	5907	6798
4 or more	28,179	2049	26,129	12,709	13,503	816	736
2 or more	1,599,751	350,458	1,249,293	642,329	790,234	58,320	66,524
1 or more	14,417,349			5,952,472	6,663,206	660,032	642,571
Prevalence percentage (crude)							
1 or more	4.54%	n.a.	n.a.	4.81%	5.28%	3.13%	2.80%
2 or more	0.50%	0.11%	0.39%	0.52%	0.63%	0.28%	0.29%
Prevalence percentage age adjusted to the US 2000 population							
1 or more	4.02%	n.a.	n.a.	4.37%	4.15%	4.41%	2.94%
2 or more	0.45%	0.10%	0.35%	0.49%	0.47%	0.44%	0.32%

48]. Table 2.6 compares the strengths and limitations for some of the most frequently used sources of data on cancer survivorship. Examples of each of these and selected key findings to date are described briefly below.

2.4.1 Clinical Trials

Clinical trials, often considered the "gold standard" as sources of data, remain a mainstay of cancer survivorship research. Because they capture detailed information on therapeutic exposure and adverse events, clinical trials data are ideally suited to assess adverse physical sequelae (persistent and late occurring symptoms and medical conditions) of care and who may be at risk for these. Long-term follow-up studies conducted among trial participants show that many otherwise curative therapies confer risk of late and sometimes fatal complications. For example, survivors whose original therapies included exposure to anthracyclines and/or chest irradiation are at increased risk of developing late cardiac complications [49].

Traditionally, cancer clinical trials have sought to compare the effect of different treatment regimens on morbidity (disease progression and recurrence) and mortality (survival) outcomes. Interventions focused on use of one or a combination of modalities: surgery, radiation, chemotherapy and/or hormonal therapy. Few of the earlier generation of trials included assessment of quality of life of survivors, and hence offered little information on a variety of survivorship outcomes. This changed with recognition by the Food and Drug Administration that quality of life could be a valid end point in a clinical trial [50], and subsequent incorporation by the national clinical trials groups of QOL measures in phase III trials [51–53].

Most research targeting the role of lifestyle, behavioral, psychosocial, economic and social factors affecting cancer survivors continues to rely on other sources of observational data because this type of information is not routinely assessed in clinical trials. Over time, however, even this is changing with the introduction of trials examining the contribution of behaviors and symptom management to disease and survival. For example, a diet and lifestyle protocol was added to an adjuvant therapy trial for stage III colon cancer comparing therapeutic drug regimens (CALGB 89803) to investigate the effect of diet midway through adjuvant therapy and again, 6 months after completion of treatment [54]. An ongoing randomized phase III trial seeks to determine whether weight loss in overweight and obese women may prevent breast cancer recurrence [55]. Further, some trialists are beginning

Table 2.6 Sources of data for survivorship research

Type of data	Pros	Cons	Example(s)
Clinical trials	Gold standard treatment data/ disease characterization information collected Usually collect biospecimens (e.g., DNA or tumor tissue) Clear chronological relationship between exposures and outcomes	Generally lacks non-treatment related data (e.g., smoking or lifestyle exposures) Not representative of the general population Expensive and resource-intensive	NCI's National Clinical Trials Network [128]
Traditional survivor cohorts	Able to measure a wide variety of patient (demographic, lifestyle, behavioral, and genomic) characteristics, co-morbidities, disease characteristics, and treatment-related outcomes Can observe late effects from treatment and outcomes with long latency and induction periods Population more representative of general US population Clear chronological relationship between exposures and outcomes May be good source of biospecimens	Pre-diagnostic information generally collected retrospectively Expensive Time-intensive Inefficient for rare outcomes and exposures May not include diverse populations	Childhood Cancer Survivor Study (CCSS), Detroit ROCS
"Converted" risk cohorts with survivorship endpoints	Usually has pre- and post-diagnostic information collected prospectively May be good source of biospecimens Clear chronological relationship between exposures and outcomes	Treatment and disease characteristics data may be lacking Large numbers are required for rarer cancers and exposures	WHI Life and Longevity After Cancer Study (LILAC)
Cross-sectional studies	Nationally representative samples Large sample sizes Can assess cancer trends in disease burden over time Data publicly available Good for hypothesis generation provides "snapshot" of prevalence of cancer risk Factors and outcomes	Cannot determine temporal relationships between exposures and outcomes	National Health Interview Survey (NHIS) Cancer Control Supplement (CCS); Health Information National Trends Survey (HINTS)
Electronic medical records from provider networks	Data often up-to-date and comprehensive of treatment and comorbid-conditions history Access to data not otherwise easily available Large sample sizes	Not collected by trained research staff: no standardization of data entry Patient privacy and confidentiality concerns	Cancer Research Network (CRN)
SEER-linked registries	Large sample sizes Data publically available Data can be linked to the Medicare database (detailed treatment information) Nationally representative samples Good for study of rare cancers	Data limited to that collected by SEER Data may be incomplete Patients who move across state lines may be counted twice/lost to follow-up Registries rely on hospital-based reporting (may underreport for outpatient therapies)	SEER-MHOS, SEER-Medicare, SEER-CAHPS
Data compiled by advocacy groups	Participants are motivated to participate in studies Often have strong response rates	Not representative of general population	Army of women

to embrace the idea of systematically capturing more descriptive, behavioral data from participants at the outset of the trial that could, as already found in one review [56], alter response to therapy (e.g., co-morbid conditions, presence of depression, level of physical activity).

A further limitation of trials data for examination of survivorship outcomes is their general lack of representativeness. According to clinicaltrials.gov, there are more than 20,000 clinical trials actively recruiting cancer patients at sites across the U.S. and abroad. Although approximately 20% of adult cancer patients are eligible for clinical trials, less than 5% of U.S. cancer survivors actually participate in clinical trials [57]. Many older adults, the majority of those diagnosed with cancer, are excluded from open trials due to concerns over co-morbid burden [58].

At the same time, concern has been raised about lower than anticipated participation of adolescent and young adults in trials, and hence their under-representation in trial outcome data [59]. The survivors that do participate in trials tend to be healthier, younger, and less ethnically, racially and socioeconomically diverse than the general U.S. survivor population due to trial eligibility requirements, access to care and concern over competing health conditions [58]. This "healthy participant" selection bias raises concern that the long-term and late effects seen among trial participants may well underestimate true incidence of complications in the general population.

2.4.2 Survivorship Cohorts

Several types of longitudinal studies are used for survivorship research. The most common involve survivor cohorts (i.e., in which participants are recruited at or following diagnosis with cancer), converted risk cohorts (i.e., cohorts of cancer-free participants originally studied for risk factors of developing cancer, or other health conditions, and then "converted" to study survivorship), and studies that follow up cancer survivors in national registries or provider networks. Cohort studies are often used to evaluate genetic, psychosocial, behavioral, economic and environmental risk factors for recurrence, progression, survival, and subsequent neoplasms in cancer survivors, as well as adverse effects from treatment (including late effects) and individual, family and societal burden of cancer. Survivor cohorts typically enroll newly diagnosed cancer survivors as close to the time of diagnosis as possible and follow them throughout their lives while collecting information about many aspects of their mental and physical health and disease history, often accompanied by biological specimens (e.g., blood and tumor tissue).

"Converted" risk cohort studies often have pre-cancer data on participants, as well as a built-in comparison group of those who do not develop cancer, which is critical to understanding the unique contribution of cancer in health outcomes. Research using cohort data shows that while they look very similar to unaffected peers at diagnosis, cancer survivors are at risk for worse physical function post-treatment than their non-cancer peers, a discrepancy that is greater for those diagnosed at a younger age [60]. At the same time, those who report being physically active before cancer and remain so after diagnosis have better survival outcomes [61–63]. Early post-treatment recruitment minimizes the potential selection bias that results from recruiting cancer survivors who have lived long enough to meet eligibility requirements (e.g., passed the 5-year survival mark thereby excluding those with more advanced or aggressive disease).

The longest running survivor cohort supported by the NCI is the Childhood Cancer Survivor Study (CCSS) [64–66]. Originally funded in 1994, this cohort, which now includes almost 36,000 survivors of childhood cancer, is comprised of individuals who were a minimum of 5-years post-diagnosis at time of study entry. The cohort also includes a sample of 5000 siblings used as controls or comparison group members for study outcomes. CCSS has proved an invaluable source of information on outcomes among long-term childhood cancer survivors. Key findings include recognition that compared to their siblings, these young survivors have an 8-fold risk of developing serious, at times life-threatening conditions by the time they reach middle age [67]; many are at risk for premature frailty/aging [68]; collectively they are at higher

risk of unemployment than their siblings [69]; and a subset may experience lower emotional well-being over time [70].

On the positive side, while rates of infertility may be somewhat elevated [71], offspring of childhood survivors do not appear to be adversely affected by a mother's history of cancer [72], and overall, most survivors are psychologically healthy and report satisfaction with their lives [73]. Because there are two generations of children treated in the cohort (1976–1986 and 1987–1999), comparison of outcome data enabled researchers to demonstrate that improvements in treatment have, as hoped, lowered risk of later cancer and functional impairment [64]. Of note, despite the evolution of treatments designed to reduce toxicities, self-reported health status among childhood cancer survivors has not improved [74]. Comparable longitudinal epidemiologic data sets do not yet exist for survivors of adult onset cancer, although efforts to create these are underway.

Establishing a cohort based on age is reasonable for the more narrowly defined range of childhood cancers, but is not feasible for adults given the large variation of types of adult cancer that exist. As a consequence, cohort studies are typically grouped by cancer site for adult cancers, such as those examining survivors of breast cancer [75–78] or colon cancer [79, 80]. A few cohorts include mixed cancers grouped by gender or race/ethnicity [81, 82]. As we learn more and technology allows for better precision, cohorts could be focused on specific treatment-related effects [83], treatment protocols [84], or disease subtypes [85, 86]. Table 2.7 lists selected survivor cohorts currently supported by the National Cancer Institute (NCI). NCI also maintains a more complete list of cohort studies available for survivorship research at http://epi.grants.cancer.gov/survivor-cohort-resources/.

2.4.3 Cross-Sectional Surveys

Cross sectional surveys provide a glimpse at a population at a single point in time and are often used to generate detailed information on trends in behaviors, health, and function in a broad array of domains. There are several publicly available

Table 2.7 Selected cohort studies for survivorship research currently supported by NCI

Cohort	Cohort size	Population	Biospecimen collection
Life and Longevity After Cancer Study (LILAC)	21,822	Women diagnosed with breast, colorectal, endometrial, lung and ovarian cancers, as well as lymphoma, leukemia, and melanoma during their participation in WHI	Formalin fixed paraffin-embedded tumor tissue, serum, plasma, blood, buffy coat, urine
PCPT and SELECT cohorts	52,603	Male prostate cancer survivors in the PCPT and SELECT prevention trials	Plasma, serum, red blood cells, white blood cells, toenails, prostate tissue
The Lymphoma Epidemiology of Outcomes (LEO) Cohort Study	12,900	NHL survivors recruited from Mayo Clinic, University of Iowa, University of Wisconsin, Emory, Miami, MD Anderson, and Cornell	Blood, plasma, buffy coat, serum
The St. Jude Lifetime Cohort	9800	5+ year survivors of childhood cancers	Tumor tissue, blood, urine, plasma, serum
Pathways: A Study of Breast Cancer Survivorship	4505	First primary invasive breast cancer survivors in the Kaiser Permanente Northern California (KPNC) system	Blood, tumor, tissue microarray slides
The ColoCare Study	4167	Patients with invasive colorectal cancer	Blood; serum; stool; saliva
Detroit Research on Cancer Survivors (Detroit ROCS)	5560 patient; 2780 caregivers	Newly diagnosed lung, prostate, breast, and colon cancer from the Detroit area and their informal caregivers	Blood, saliva FFPE tumor tissue
The Boston Lung Cancer Survival Cohort	11,164	Lung cancer survivors diagnosed at the Dana Farber Cancer Institute or Mass General Hospital from 1992-present	Tumor/non-tumor tissue; serum; DNA and urine

cross-sectional surveys supported by the Centers for Disease Control and Prevention (CDC) and NCI/NIH that serve as a source of information on specific aspects of cancer survivorship such as health beliefs and behaviors, healthcare utilization patterns, communication needs, and costs of care. These include: the Behavioral Risk Factor Surveillance System (BRFSS), National Health Interview Survey (NHIS), Medical Expenditure Panel Survey Experiences (MEPS) Cancer Survivorship Supplement, and Health Information National Trends Survey (HINTS) [87–89].

BRFSS and NHIS, which serve as a source of population-based data on cancer prevention (tobacco use, nutrition, physical activity, alcohol use, and obesity) and early detection (mammograms, Pap tests, and colorectal and prostate cancer screening tests), have had items added to better assess the cancer survivors' experience. BRFSS has created the option for states to include the Cancer Survivorship Module, which measures follow-up care (who is providing the care and where), treatment plans, and pain management. NHIS fielded a separate cancer survivorship module as part of the cancer control supplements in both 1999 and 2010.

Analyses of these latter data found poor physical and mental health-related quality of life were reported by 24.5% and 10.1% of survivors respectively, compared with 10.2% and 5.9% of adults without cancer, which represents a population of approximately 3.3 million and 1.4 million U.S. survivors with poor physical and mental health respectively [90]. MEPS, given to a selected group of prior NHIS participants, focuses on health care utilization and costs by asking cancer survivors about the financial costs of cancer, access to health care, ability to work and physical functioning, and use of prescription drugs. Using MEPS data, Guy and colleagues found that cancer survivors were more likely to have chronic conditions and multiple chronic conditions than those without a cancer history, which in turn have implications both for financial well-being and care [91]. NCI's HINTS survey, fielded annually, collects nationally representative data about the American public's use of and attitudes towards cancer-related information. HINTS data suggest that despite greater attention to survivorship, communication challenges persist. One third to one half of survivors report suboptimal patient-centered communication, particularly on such core functions of providers as helping to manage uncertainty (48%) and responding to emotions (49%) [92]. It is important to note that cross-sectional studies cannot be used to establish causality, but they do provide valuable information about the current landscape of survivorship.

2.4.4 SEER Based or Linked Platforms

National cancer registries, the cornerstone of cancer prevalence estimates, and a vital resource for clinical, demographic, and cause of death information on cancer survivors, can be used to identify participants for survivorship studies. The advantage of recruitment through registries (versus cancer centers or local treating facilities) is that it affords population-based sampling. SEER-generated studies have included single cancer populations [93, 94], multi-site samples [95, 96], and even age-grouped samples [97]. In principle, registry recruitment would also permit sampling by race/ethnicity, geography, and the extent of disease at diagnosis. Using SEER registry data, the Prostate Cancer Outcomes Study was among the first to demonstrate the long-term consequences of curative therapy, and that men experienced distinct patterns of bladder, bowel and sexual dysfunction dependent upon the type of treatment received [98].

In addition to serving as a potential recruitment platform, NCI maintains several large databases with linkage to SEER cancer registry data that are particularly relevant for survivorship research: (1) SEER-Medicare with detailed data about Medicare claims for Medicare beneficiaries with cancer, (2) SEER-CAHPS that links SEER data with Medicare Consumer Assessment of Healthcare Providers and Systems (CAHPS®) patient surveys, and (3) SEER-MHOS that provides detailed information about elderly persons with cancer who completed the Medicare Health Outcomes Survey (MHOS) that provides information about the health-related

quality of life (HRQOL) of Medicare Advantage Organization (MAO) enrollees.

These data sources can be used for an array of epidemiological and health services research including patterns of care studies, understanding Medicare beneficiaries' experiences with their care, and their HRQOL across the cancer care continuum [25, 31, 99–101]. In a large SEER-MHOS study comparing function on the Short Form Health Survey of over 16,000 survivors of diverse cancers with that for over 1 million individuals without a cancer diagnosis, Kent and colleagues found that survivors had significantly worse physical health status. While mental health was comparable, scores for the Role-Emotional and Social Functioning scales were worse for patients with most types of cancer versus those without cancer [25].

2.4.5 Other Resources

Healthcare delivery systems and provider networks provide additional platforms for survivorship science. Most contain sources of data that extend for long periods before, during, and after a cancer diagnosis that can be used to address studies of cancer etiology, treatment, outcomes, and financial costs. For example, the HMO Cancer Research Network (https://www.crn.cancer.gov/), an NCI-funded consortium of health care delivery sites with over 8 million enrollees has been used to examine surveillance, predictors of recurrence, healthcare delivery and care coordination, health care utilization and costs, psychosocial outcomes, cancer communication and decision making, late effects of cancer and its treatment, use of and adherence to adjuvant therapies, and lifestyle and behavioral interventions following cancer treatment [102, 103]. Cohort studies of breast cancer survivors have also been recruited through the Kaiser Permanente provider networks in Northern California (San Francisco, Bay Area, Sacramento) [75, 85]. It is noted that healthcare provider and delivery system platforms by definition exclude un-insured persons, and may not represent lower income populations. Further, it can be difficult to track over time those who change insurers or move locations.

In addition to helping patients, their families, and their caregivers navigate the cancer landscape, many patient advocacy groups are entering the research arena, encouraging the generation of important survivorship data by organizing networks of ready participants (e.g., Livestrong's platform, Susan Love's Army of Women, American Cancer Society's Cancer Survivors Network) [104–106]. While these groups are critical to boosting study participation, data provided must be interpreted with caution as participants typically represent the most motivated patients and often fail to reflect the views, status or outcomes for the general cancer survivor population.

2.4.6 Collaborations

Because of the expense of maintaining survivor cohorts, growing efforts are being directed toward leveraging existing data wherever possible [107, 108]. There are several resources provided by NCI to facilitate collaborations available online (https://cancercontrol.cancer.gov/ocs/resources/researchers.html). Regardless of the study design used, most investigators continue to be challenged by concerns over which measures to include in a given study, trying simultaneously to balance the temptation to assess a broad spectrum of topics that affect cancer survivors, all without overburdening study participants and staying within realistic time and resource constraints [107]. The survivorship research community has a long history of interdisciplinary collaboration and sharing data to augment existing resources and generate enough statistical power to answer important research questions, especially for minority populations and rarer cancers.

Use of validated, established measures across studies facilitates future data sharing by making data harmonization possible. Several tools now assist in selecting high quality and appropriate measures, including: the FACT set of measures [109]; *Patient-Reported Outcomes Measurement Information System (PROMIS)* for tools that

measure PROs such as pain, fatigue, physical functioning, emotional distress, and social role participation [110], Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE), a PRO measurement system developed to characterize the frequency, severity and interference of 78 symptomatic treatment toxicities [111], and the PhenX Toolkit for population-based genomic studies [112].

2.5 Future Directions

Looking to the future, pursuit of initiatives in several arenas will be necessary if we are to advance the epidemiology of cancer survivorship. First among these is the development of platforms or datasets that will allow us to better characterize the national population of cancer survivors. Our current inability to better describe and project the burden of cancer on the larger population makes planning for the future care of today's and tomorrow's survivors a significant challenge. It also makes it harder to mark the progress being made to improve not just the length of survival, but importantly the quality of life and function of those living long term with a cancer history.

Efforts are already underway to enhance, through both expanded data acquisition and targeted linkages, the capacity of SEER registries to capture more detailed information about the prevalent population, how they are treated and continue to be treated medically, where they are on the cancer trajectory, and how they are faring physically, emotionally, socially and economically. Investment in cancer survivor cohorts, either de novo (e.g. Childhood Cancer Survivor Study, Pathways study) or as follow-on subsets of those recruited for standard cancer epidemiologic (risk) cohorts (e.g., WHI) will serve as a rich complement to the registry data by providing ongoing access to survivors for assessment of unique survivorship outcomes (e.g., prevalence, patterns and persistence of fatigue, impact of survivorship on economic outcomes), and in terms of the latter cohorts, by enabling comparison of the health and function of survivors, versus their peers without a cancer history.

Regardless of setting, whether registry-based populations or cohorts, finding improved methods for addressing pre-existing and post-cancer incidence and impact of co-morbid illnesses must be pursued. At present, there is limited agreement about how best to approach this task [113]. Lack of a standard approach to measuring the presence and burden of co-morbidity makes it difficult to tease apart conditions or loss of function that may have pre-dated the cancer, been exacerbated by cancer or its treatment, are simply a function of aging, or as some worry is the case, may be the consequence of pre-mature or accelerated aging among survivors.

Depending on uptake of these technologies, and notwithstanding real issues with their interoperability, electronic health records could prove a boon to survivorship science. Searchable datasets with linked healthcare information on patients treated may prove a rich resource for cancer epidemiology in the future. Similarly, the mandate by the American College of Surgeons Commission on Cancer for accredited hospitals and centers to develop and deliver survivorship care plans, suggests that more detailed treatment exposure information and recommended care will be systematically documented for a growing population of survivors. The utility of this information, however, will depend wholly on compliance with documentation, and the type and quality of the data entered. For example, a simple yes/no response to whether a survivorship care plan was delivered to the patient tells us nothing about what may have been in this document, happened at the time of the exchange, or could be expected to make a difference in patient or provider behavior going forward.

Given the growing importance of post-treatment care for cancer survivors, attention is also needed to characterizing and monitoring the diverse pathways to recovery and their contribution to survivors' long-term health. If we are to find the most efficient, effective, equitable and available ways to care for survivors, investment in efforts to define and monitor adherence to different models of care for populations of survivors will be important. Research within healthcare delivery systems (such as that previously funded

by NCI under the Cancer Research Network or CRN) could help advance our understanding of what works best, for whom, and the cost of delivery of this care. While other countries have developed risk-based algorithms for care post-treatment (e.g., the UK and Australian models), this has yet to be embraced in the U.S. However, analysis of data from extant integrated care provider systems, as well as that being collected in the CMS Oncology Care model sites, could inform our understanding of optimal care trajectories.

A final challenge for cancer epidemiology broadly is ensuring that we are learning about representative samples of Americans and other well specified groups around the world. It is clear that significant—and potentially growing—health disparities in cancer survival (as noted earlier) and cancer survivorship outcomes exist for diverse segments of the population based on race/ethnicity, education, geography, age, sexual orientation and gender identity, income and/or other barriers to access to quality care [114–116]. Documenting and tracking the experience of these populations within and across countries will be important if we are to develop and determine the effect of targeted interventions to address observed disparities in survivors' outcomes.

Looking to the future, we would like to close by reflecting on a final emerging epidemiologic issue, often overlooked in addressing cancer survivorship, and that is the characterization and monitoring of the emerging population of cancer caregivers. Largely family members, and sometimes referred to as secondary or co-survivors, these individuals are included under the rubric of 'cancer survivor' promulgated by the advocacy community (see Box 2.1). Caregivers are frequently 'in the room' with their loved one and influence decisions and affect care. They provide vital emotional and tangible support as well as direct care, including oversight of medication, doctor's visits, and wound care. Importantly, their numbers, like those for survivors, are growing.

The population of cancer caregivers, already encompassing an estimated 2.8 million individuals is expected to continue to grow as the number of survivors rises [117]. Of note, as the majority of caregivers are spouses, this population will also be older, paralleling the aging of the projected cancer survivor population. The trajectory of cancer caregiving is different than care for those without cancer. It tends to be more intense and episodic, and may demand greater capacity for medical management and decision-making [117]. Based on available data, the majority of cancer caregivers are females, many of who may work as well as provide caregiving to minor children [118]. In terms of this latter, it is estimated that over 1.58 million U.S. cancer survivors reside with their minor children [119]. Cancer caregivers often report feeling ill-prepared for their roles and may neglect their own health in the process of caregiving [120]. Cancer can have a negative impact on caregiver employment and family finances [121]. Research also demonstrates that the well-being of survivors and their caregivers often parallel one another [118, 122, 123]. The mutuality of this relationship has led investigators to suggest that interventions to address caregiver needs may also benefit their care recipient [124, 125].

If we are to truly track and address the burden of cancer for survivors, we must include in this effort surveillance of the physical, psychological social and economic health and function, as well as the healthcare utilization of, the growing caregiver population. One challenge to such an effort is finding reliable ways to define who constitutes a caregiver. Many spouses do not think of themselves as caregivers. For their part, survivors vary in who they identify as serving in this role, which latter may shift over time as reflecting the fluctuation in needs to be met based on where a person is in the illness and recovery trajectory. In a rare attempt to document the impact of cancer on these secondary survivors, the American Cancer Society launched its cancer caregiver cohort in 2006 enrolling almost 900 caregivers and following them at 2, 5 and 8-years post-diagnosis of cancer in their loved one [126, 127]. The recently NCI funded Detroit cohort (see Table 2.7) includes a cohort of caregivers matched to its survivor sample. While valuable, we need to augment these resources with nationally

representative samples to better understand and track the burden of this care for caregivers themselves as well as the nation.

2.6 Summary

The past two decades have witnessed dramatic advances in the epidemiology of cancer survivorship, including our understanding of who comprise the current population of cancer survivors, and how they are faring. We have tried across this chapter to identify a number of pathways to build upon what we already know, while simultaneously addressing important gaps in our knowledge base. In terms of maturation, the field of cancer survivorship research is now firmly in its young adulthood. Moving forward, pressure will be on to take the lessons learned from the epidemiology of the disease, to design, test and deliver interventions with the capacity to reduce current levels of cancer-related morbidity and pre-mature mortality. The ultimate goal will be to use the epidemiologic knowledge generated to enhance not simply the length of survival for those diagnosed, but as importantly, the quality of life of all cancer survivors and their caregivers.

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Adjustment to Life as a Cancer Survivor

3

Timothy J. Williamson and Annette L. Stanton

3.1 Introduction

> "*When treatment was over, I expected to be done with cancer. My family expected me to feel better. Wow, were we wrong.*"
> "*The first time I was asked to write about the positive aspects [of the cancer experience] for 20 minutes, I thought, 'Are you kidding?' Then as I started thinking about it I was amazed at all of the things that came to mind!*"
> "*The past year has been a roller coaster ride … It's hard to express these feelings of frustration, sadness, anger, bitterness, and disappointment. I'm never feeling just right, with so many changes going on in my body. Every twinge or pain brings fear. How fragile life is. How do I move on?*"
> "*I feel so grateful each morning to wake up in my bed and feel so good and alive and eager to face another day.*"

From individuals diagnosed with cancer who had recently completed primary oncologic treatments and were taking part in the author's (ALS) research, these sentiments clearly demonstrate that "one size does not fit all" when it comes to the experience of cancer and its subsequent management. Although heterogeneity is marked, the body of relevant research illuminates several themes related to cancer survivors' quality of life and health following primary treatments for cancer. The primary focus of this chapter is on research regarding the experiences of adult cancer survivors as they adapt to life following diagnosis and primary treatment. After a consideration of terminology and the phases of cancer survivorship, this chapter is devoted to characterizing that literature. Suggestions for future research are also provided.

3.2 The Language and Nature of Cancer Survivorship

According to the National Cancer Institute (NCI), "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" [1]. This expansive definition makes two important points. First, cancer affects not only individuals but also their interpersonal circles, as addressed by other chapters in this volume. Second, all phases of the cancer trajectory deserve public and professional attention, including the experience of diagnosis, initial treatments, the re-entry phase immediately after those treatments are completed, extended survivorship, and advanced disease.

The NCI's definition of survivorship is not uniformly adopted by professionals or the public, however. The terms used by people to describe

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their own status vary markedly [2]. Whereas some adults diagnosed with cancer proudly call themselves survivors (either immediately or after a span of time), not all choose to self-identify as such and some actively dislike the term, believing that it connotes cancer as an invariably traumatic experience, for example [3]. Still others who are living with advanced cancer can find the term unfitting and believe that it diminishes the gravity or chronicity of their condition. In conducting research with people living with metastatic cancer, one author (ALS) found that some participants had strong and varied reactions to the descriptors "survivor," "Stage 4," "advanced," and "metastatic." Clinically, listening for and acknowledging the preferences of individuals in labeling their own status conveys respect [4]. In this chapter, we use the term "survivor" while acknowledging its limitations.

We focus this chapter on the phases of the cancer trajectory that extend beyond the receipt of treatments typically intended as curative, which include—alone or in combination—surgery, radiation treatment, chemotherapy, and other biologic therapies. The establishment of the National Coalition for Cancer Survivorship in 1986 and the NCI's Office of Cancer Survivorship in 1996, as well as two landmark publications by the Institute of Medicine [5, 6], stimulated intense interest among scientists, clinicians, and the public in the unique medical and psychosocial experiences and needs of individuals during the post-treatment phases.

3.3 Phases of Cancer Survivorship

The often-lengthy period following primary oncologic treatment completion can be distinguished into the (1) re-entry, (2) early survivorship, and (3) long-term survivorship phase, for which the boundaries are not sharply demarcated. The re-entry phase [7] often encompasses the year (or more) after treatment completion in which adults make the psychosocial transition from "cancer patient" to "person with a history of cancer." When individuals (and their loved ones) are not prepared by health care professionals for this period, they can be surprised by their feelings as treatment ends. These individuals can hold unrealistic expectations for quick recovery [5]. In the words of a physician describing her own experience, "I thought I would feel happy about finally reaching the end of treatment, but instead, I was sobbing…Instead of [feeling] joyous, I felt lonely, abandoned, and terrified. This was the rocky beginning of cancer survivorship for me" [8]. The re-entry phase commonly involves a perceived loss of the safety net of active treatment and frequent oncologic appointments, resumption or revision of major life roles, a decline in interpersonal support, and the experience of lingering or emerging effects of diagnosis and treatment [5, 9]. Although the diagnostic and treatment phases are associated with the most serious psychological impact, research suggests that a substantial minority of survivors experience an increase in distress during the re-entry phase [10] and beyond [11].

The early survivorship period extends from the re-entry phase through roughly 5 years after diagnosis. In those years, cancer and treatment-related physical and psychological morbidities tend to resolve for most survivors, although they can arise or persist in others. Cancer survivors often experience "islands" or periods of psychosocial disruption after they have recovered from primary treatments [12]. In other words, for some, cancer survivorship can be periodically or persistently a challenge throughout life [11]. Follow-up appointments for cancer surveillance can prompt elevated fear of cancer recurrence. Additionally, the survivor might fear that any troubling symptom or functional decline signals cancer recurrence when in fact it could indicate the natural process of aging.

During long-term survivorship beyond 5 years after diagnosis, quality of life of adults on average is indistinguishable from that of the general population [13–15]. Just as the 5-year post-diagnosis marker of survival in oncology does not guarantee that cancer is cured, a 5-year indicator of long-term survivorship does not imply that psychological or physical recovery is complete. For example, a population-based longitudinal study of 1,288

prostate cancer patients from 6 to 12 months after diagnosis through 5 years demonstrated that the majority of men reported no significant problems and improvement in sexual and urinary function from 6 months to 5 years after diagnosis [16]. However, 10% and 14% of men reported incontinence at 2 years and 5 years, respectively, and 22% and 28% had erectile problems. Population-based studies also indicate greater activity limitations, poorer health status, higher medical expenditures, and greater indirect costs of morbidities (e.g., lost productivity) in survivors' years after diagnosis relative to adults with no cancer diagnosis [17, 18]. It is important to keep in mind that a minority of survivors contends with toxic physical and psychological effects even many years after diagnosis [14, 15, 19–21].

An important point is that people with cancer also can experience recurrence of the primary cancer, another primary cancer (i.e., an unrelated malignancy), or metastatic disease. An initial or later diagnosis of metastatic disease indicates poorer prognosis, although complete remission is possible in particular cancers (e.g., testicular). In addition, metastatic cancer is increasingly being considered a chronic rather than a rapidly terminal disease, often spanning many years and involving a series of oncologic treatments.

Finally, the present characterization of the experience of adults who are beyond primary treatment completion is not meant to imply that ongoing therapies, such as the endocrine therapies prescribed for estrogen receptor-positive breast cancer (e.g., tamoxifen), should be considered ancillary rather than indicated as a life-preserving approach. We are not aware of published research on whether the oncology team prescribing tamoxifen as an important component of treatment from the outset of treatment planning or as an option presented shortly before it is prescribed has consequences for women's perceptions of its necessity, which are known to influence adherence to medication regimens [22].

We recommend that researchers and clinicians consider the relevance of the language of cancer survivorship in their work with research participants and patients. It can be challenging to strike a balance in the use of precise language, standard terminology in the medical and psychosocial oncology literature, and terms preferred by people living with a cancer diagnosis.

3.4 Adaptive Tasks Following Cancer Diagnosis and Treatment

Within a decade following the publication on Cancer Treatment and Survivorship Facts and Figures 2016–2017 by the American Cancer Society, more than 20 million people in the United States are expected to be living with a prior incident diagnosis of cancer [23]. Commonalities in their experience can be conceptualized as the adaptive tasks of survivorship [24]. As displayed in Table 3.1, a first set of adaptive tasks pertains to the medical and physical health domains. These challenges include: (1) coming to understand that treatment completion often does not signify the end of physical morbidities; (2) finding accurate and useful resources for contending with symptoms; (3) balancing the common desire for continued medical care by the oncology team with the necessity of returning to the primary care setting [6]; and (4) engaging in extended cancer surveillance and behaviors to lower the likelihood of recurrence and metastasis, such as adhering to endocrine therapy or recommended physical activity. Particularly problematic symptoms include the persistent fatigue reported by one-quarter to one-third of survivors through 10 years after cancer diagnosis [25] and the 15–25% rate of cognitive problems associated with chemotherapy or brain irradiation in the reentry and early survivorship periods, which can persist over the longer term [26].

Managing psychological consequences is a second adaptive task that often extends into reentry and extended survivorship. It is not uncommon for the psychological impact to become manifest once the acute phases of diagnosis and the most demanding treatments, which can command the entirety of one's physical and psychic energy, are completed. Meta-analytic findings demonstrate that the prevalence of depression is

Table 3.1 Adaptive tasks following cancer diagnosis and treatment

Domain	Examples and descriptions
Physical/ Medical	• Coming to understand that treatment completion often does not signify the end of physical morbidities • Finding accurate and helpful resources for managing ongoing physical symptoms (e.g., neuropathy, pain, fatigue) • Navigating the desire for continued medical care by the oncology team with the need to return to the primary care setting • Engaging in extended cancer surveillance and behaviors directed toward lowering the likelihood of recurrence and metastasis (e.g., physical activity, adherence to endocrine therapy for breast cancer)
Psychological	• Managing psychological consequences (e.g., depressive symptoms) of the cancer experience through cognitive (e.g., reappraisal), emotional (e.g., expression of feelings) and behavioral (e.g., progressive muscle relaxation) strategies • Seeking mental health services • Addressing fears of cancer recurrence or metastasis
Practical/ Vocational/ Financial	• Deciding if and/or in what capacity one will return to work • Managing financial consequences of cancer and its treatment
Existential/ Spiritual	• Addressing existential questions about the meaning or significance of the cancer experience in the context of the survivor's life • Finding benefit (e.g., strengthened interpersonal relationships, deepened purpose in life) in the cancer experience
Interpersonal	• Navigating declines in support provided by the social network and medical team • Managing expectations from friends and family for the cancer survivor to resume all prior roles and responsibilities rapidly

highest during treatment relative to the first year after diagnosis and thereafter [27]. Although a diagnosis of cancer certainly can provoke anxiety, cancer-related post-traumatic stress disorder (PTSD), as assessed via diagnostic interview or validated questionnaire, typically is evident in less than 10% of adult cancer survivors after treatment completion, and it decreases over time (e.g., [28]). Specific fears regarding the potential for cancer recurrence are among the most commonly experienced psychological sequelae [29] and are related to survivors' higher use of medical services [30]. In a systematic review, researchers found that most long-term survivors experience modest to moderate levels of fear of recurrence [31].

Attending to practical concerns is a third adaptive task after treatment completion. For example, interviews with survivors one to 5 years after diagnosis indicated that 39% of women and 41% of men stopped working during treatment [32]. The large majority returned to work during the re-entry phase, and the projected rate of return to employment at 4 years was 84%. However, 21% of women and 16% of men reported cancer-related limitations in the ability to work. Nearly one-third of survivors reported cancer-related financial problems in a population-based study, and they were more likely than survivors without financial concerns to forego or delay recommended medical care, including mental health care [33].

A fourth adaptive task involves addressing existential questions regarding the meaning of the cancer experience in the context of the survivor's life. The majority of survivors of various cancers report finding some benefit in their experience (also studied as "posttraumatic growth" [34]; see [35–37] for reviews). Major domains of perceived benefit include deepened interpersonal relationships, increased commitment to life priorities, heightened appreciation for life, augmented self-regard, enhanced spirituality, and increased attention to health behaviors. Longitudinal research suggests that finding benefit in the cancer experience increases from the diagnostic and treatment phase through re-entry and early survivorship [38, 39]. Long-term survivors also report benefit [40, 41], although finding benefit may decrease years after treatment completion [42]. Research indicates that promoting cancer-related benefit finding through writing

can boost positive psychological and physical health-related outcomes after treatment completion [43], and a group-based psychotherapeutic intervention protocol is being tested to promote benefit finding among breast cancer patients varying in time elapsed since diagnosis [44].

Finally, another set of adaptive tasks pertains to negotiating interpersonal relationships. The declines in support provided by the medical team, family, friends and co-workers that can accompany the completion of oncologic treatment can be difficult, particularly in survivors who encounter lingering or emerging cancer-related problems. Familial expectations for life to return rapidly to normal and for the cancer survivor to resume all prior responsibilities and roles also can weigh heavily on the survivor. Relationships with friends change. Following cancer treatment, survivors may revise their priorities to concentrate on relationships that are the most meaningful.

In summary, adaptive tasks of cancer survivorship can span nearly every facet of the lives of people living with the diagnosis. Effective management of cancer's multiple demands and the ability to derive benefit from the experience are evident in most survivors. Problems of survivorship improve or resolve during re-entry and early survivorship in most but not all cases. Factors relevant to resolution or exacerbation of problems are addressed in the next section. This chapter and others in this handbook review many of the adaptive challenges in greater detail.

3.5 Sociodemographic Factors Associated with Adjustment

As summarized in Table 3.2, several sociodemographic characteristics have been investigated with regard to their associations with adjustment to cancer. In the following section, we provide an overview of the factors that have

Table 3.2 Correlates of favorable adjustment to cancer

Characteristic	Relationship to adjustment
Younger age	• Greater difficulty with social role conflict and returning to work • Higher psychological distress • More concerns about reproductive health, sleep difficulties, and financial problems
Older age	• Worse physical quality of life • More functional difficulties
African American race or Hispanic ethnicity (vs. non-Hispanic White)	• Poorer global quality of life • Higher psychological distress • Poorer patient-provider communication
Female gender (vs. male)	• Higher psychological distress
Lower socioeconomic status	• Poorer global, psychological, and physical quality of life
Higher social support	• Higher global, psychological, and physical quality of life • Greater ability to find benefit from the cancer experience
Greater social isolation	• Poorer global, psychological, and physical quality of life • More social role disruption, pain, fatigue • Higher depressive symptoms
More social constraints	• More intrusive thoughts • Poorer physical functioning • More avoidance-oriented coping • Poorer spousal communication • Higher negative affect and psychological distress
Higher stigma	• Higher psychological distress • Higher depressive symptoms

(continued)

Table 3.2 (continued)

Characteristic	Relationship to adjustment
Higher neuroticism	• More anxiety • Higher depressive symptoms • Poorer global, psychological, and physical quality of life
Higher optimism	• Better global quality of life • Better cognitive functioning • Greater use of approach-oriented coping • Higher coping flexibility • Higher perceived social support • Less pain • Lower psychological distress
Greater use of approach-oriented coping strategies	• Higher positive affect • Better physical and psychological quality of life • Higher perceived social support • Higher vitality • Fewer medical appointments for cancer-related morbidities • Greater ability to find benefit from the cancer experience
Greater use of avoidant-oriented coping strategies	• Higher intrusive thoughts • Poorer psychological and physical quality of life • Higher physical symptom bother
Higher sense of meaning and purpose	• Less psychological distress • Better global, psychological, and physical quality of life
Higher spiritual well-being	• Greater ability to find benefit from the cancer experience

Note: The relationships displayed in this table provide an overview of empirical findings but do not represent a comprehensive or systematic review

garnered considerable attention, noting that the intersectionality or combination of these factors in their influence on adjustment in cancer survivors is understudied [45]. These factors can be readily assessed and can help medical professionals identify who may need supportive care (e.g., referral to a psychologist on the medical team).

3.5.1 Age

Many researchers have examined whether age at diagnosis relates to adjustment for survivors of adult cancers. In one study of more than 10,000 cancer patients, younger age at diagnosis was associated with poorer psychological adjustment across most cancer types (e.g., breast, bone, head and neck [46]). There was no significant relationship between age and adjustment for those with poor-prognosis cancers, likely because distress was universally high among these patient groups [46]. The relationship between younger age and greater distress is documented most consistently among breast cancer survivors. For example, a review of 42 studies specifically examining psychological distress in breast cancer survivors indicated that younger age was associated significantly with greater distress [47]. Additionally, a systematic review of 28 studies showed that younger breast cancer patients (<50 years of age), compared to older patients, reported more depressive symptoms and more concerns about menopause, menopausal symptoms, and infertility [48].

The relationship between age and other indicators of quality of life, however, is less clear. Systematic reviews indicate that age is inconsistently related to poorer overall health-related quality of life among colorectal cancer [49] and melanoma survivors [50]. Studies in which specific domains of quality of life are analyzed as separate outcomes do reveal several significant relationships. For example, in a sample of more than 6,000 patients across several cancer types, older age was related to more problems with physical functioning, constipation, and appetite loss, whereas younger age was associated with more financial problems, insomnia, and problems with social and role functioning [51]. Older cancer survivors have more medical comorbidities than their younger counterparts and face

associated challenges to physical adjustment, perhaps compounded by cancer diagnosis and treatment. By contrast, younger cancer survivors likely experience greater difficulty in social and family roles, such as raising children, returning to work, and being concerned about reproductive health (e.g., early menopause for women, impotence for men). Therefore, examining age as a predictor of global quality of life may obscure important age-related differences within specific quality of life domains. Additionally, the type of cancer and oncologic treatment received likely influences associations between age and adjustment. For example, individuals with poor-prognosis cancers may experience relatively high levels of distress regardless of age [46]. The distinct experiences of older and younger cancer survivors should be examined in greater depth, both to reveal the underlying processes linking age to poorer outcomes and to develop targeted and maximally effective supportive care efforts.

3.5.2 Race/Ethnicity

Considerable research demonstrates that African American and Hispanic/Latino cancer survivors, compared to their non-Hispanic white counterparts, experience poorer quality of life and more psychological distress [47, 52–54]. Several studies indicate that Black and Hispanic/Latino, compared to non-Hispanic white cancer patients, evidence lower health literacy [55, 56], report less trust in the medical system [57, 58], and report worse patient-provider communication [59, 60]. These factors, which perhaps have socio-structural roots, contribute to racial and ethnic differences in stage of presentation for cancer screening [55] and may also explain, in part, differences in adjustment. One study indicated that African American, compared to non-Hispanic white, women experienced longer diagnostic and treatment delays for breast cancer [61], which may explain in part the racial/ethnic disparity in mortality rates for breast cancer survivors. It is also notable that African American and Hispanic/Latino, compared to non-Hispanic white, cancer survivors are more likely to cope through turning to religion [62, 63], and some report that the cancer experience has strengthened their faith [64]. Additionally, studies indicate that spiritual coping can confer health benefits for Black and Hispanic/Latino cancer patients [65]. Finally, relationships of race and ethnicity with adjustment to cancer are often intertwined with socioeconomic status (SES). Statistically, researchers can control for SES to examine unique contributions of race and ethnicity, but doing so can limit findings' ecological validity. Rather than investigating them in isolation, researchers investigating the relationships of race, ethnicity, SES and other characteristics such as gender on adjustment, may unveil intersectional influences on health outcomes [66].

Additional research identifying factors that protect against negative outcomes is needed. It is important to consider the potentially unique strengths and needs of racial and ethnic minority populations and to produce a more comprehensive portrait of how cultural influences are related to adjustment in the cancer context. Culturally-competent interventions that harness effective processes to promote psychosocial equity also are warranted.

3.5.3 Gender-related Processes

Theory and evidence suggest that gender-related processes are influential in the course of adjustment to cancer [45, 67]. In the general population, women perceive their health to be poorer than do men [68]. Among cancer patients and caregivers, women report higher distress regardless of whether they are the affected patient or the caregiver [69].

Most research in psychosocial oncology has focused on breast and prostate cancer, which are the most frequently diagnosed cancers in women and men [70], precluding direct gender-related comparisons. Reviews of psychosocial adjustment to other cancers, however, provide additional insight. In melanoma survivors, women reported lower psychological (but not physical) quality of life than men [50], and the evidence is inconsistent regarding gender differences in overall quality of life in colorectal cancer patients [49]. Additionally, women, compared to men, with Hodgkin lym-

phoma reported worse sexual functioning [71], as well as more psychological distress and poorer quality of life [72].

Overall, findings suggest that women report poorer adjustment during cancer treatment and following treatment completion, particularly in the psychological domain. Gender roles (e.g., women socialized towards helping others, incorporation of societal attitudes about femininity) and gender-linked traits (e.g., agency or "focus on the self and separation", communion or "focus on others and connection") [71, p.131] can influence observed gender differences in adjustment to cancer [73, 74]. For example, women (and men) who strongly prioritize caring for others over self-care might be particularly likely to experience fatigue during arduous treatments. Whether cancer-related burdens amplify the gender differences in psychological functioning that are seen in the general population is not clear. Future research should examine gender roles and gender-linked processes as factors that explain group-based gender differences in adjustment to cancer.

3.5.4 Socioeconomic Status

Low SES (indicated by income, employment, education, or a combination) is consistently linked with poorer adjustment to cancer [75, 76]. In the general population and in cancer survivors, low SES is related to poorer adjustment through several direct and indirect pathways, including risky environmental factors (e.g., noise disruption preventing restful sleep, crime), lower psychological resources (e.g., optimism), restricted access to high-quality health care or adequate insurance coverage, and more frequent exposure to stressful events [49, 77–79]. Cancer survivors also can face risks of unemployment [80], and they report more days lost from work [81] than the general population, which can contribute to downward mobility. Future research should investigate whether coordinated care interventions and other efforts that reduce financial and/or transportation burden can reduce SES-related disparities in adjustment to cancer.

3.6 Interpersonal Influences on Adjustment

There are many social influences on psychological adjustment to cancer [45, 82]. Social relationships are helpful, supportive, and a source of comfort in some instances and sources of stress in others. In this section, we focus on social support as a potentially positive influence and on isolation, social constraint, and stigma as potentially negative influences on psychosocial adjustment.

3.6.1 Social Support

Social support is comprised in part from the structural aspects of one's social network as well as the perceived availability of emotional, instrumental, or informational resources [83]. Robust relationships between social support and health have been demonstrated in the general population [83–85]. Social support is theorized to influence health by buffering threat-related illness appraisals, encouraging healthy behaviors, and attenuating physiological reactivity to stress [83]. For example, cancer survivors may worry less about their cancer if they are able to share their concerns with loved ones who respond empathetically.

Consistent evidence indicates that cancer survivors' perceptions of greater social and emotional support are related to favorable psychological and physical adjustment [82, 86, 87]. For example, perceived social support longitudinally predicted higher overall quality of life among breast cancer survivors between 6 and 10 years following treatment completion [88]. Social support can improve or worsen during the course of cancer survivorship [89], with some evidence suggesting that social support declines after treatment completion [90]. Longitudinal research is needed to characterize psychosocial predictors that bolster social support for those most in need. With regard to clinical applications, oncology team members should assess the availability and effectiveness of survivors' social support. For example, a physician might ask how family and friends could help a breast cancer

survivor adhere to an endocrine therapy regimen; at the same time, the medical team could devote particular attention to survivors who have little support from others.

3.6.2 Social Isolation

Isolation may be assessed through reports of lifestyle (e.g., being unmarried, living alone, having few social contacts) or patient-reported perceptions of isolation (i.e., loneliness). Meta-analytic findings indicate that both objective and perceived isolation predict mortality in the general population [91], statistically controlling for a number of other links to mortality. In one study, occupying a fewer number of social roles prior to a breast cancer diagnosis longitudinally predicted poorer quality of life, less vitality, worse physical function, and more social role disruption between 2 and 6 years later, over and above medical treatment and tumor characteristics [92]. Feelings of loneliness also are consistently related to poorer psychological functioning in cancer survivors generally [93] and are associated with pain, depressive symptoms, fatigue, and dysregulated immune function among breast cancer survivors [94]. Social isolation likely confers risk through behavioral, cognitive, and physiological pathways [83]. For example, a socially isolated cancer survivor who has persistent fatigue might have trouble completing role responsibilities, whereas someone with supportive friends may be able to rely on them to share responsibility for tasks.

3.6.3 Social Constraints

Several studies address the ways in which unsupportive social interactions confer risk for poor adjustment to cancer. Social constraint, defined as interactions that prevent the individual with cancer from discussing the illness or expressing cancer-related thoughts and feelings [95], is one such unsupportive interaction that can relate to maladjustment to cancer both during and following treatment completion. For example, prostate cancer survivors who felt socially constrained (e.g., being ignored or excluded from one's social network when seeking support), compared to unconstrained survivors, evidenced the strongest relationship between cancer-related intrusive thoughts (e.g., unwanted thoughts about possible recurrence) and poor psychological quality of life. Constraints were associated with a greater use of avoidant coping strategies (e.g., trying to avoid cancer-related thoughts and feelings), which in turn predicted poorer psychological outcomes [95]. Constraints are also related to more negative affect, lower well-being, and poorer spousal communication among breast and lung cancer patients [96, 97]. Feeling constrained in the ability to process and express cancer-related thoughts and feelings is posited to prompt survivors' negative illness perceptions and unhelpful coping strategies, which in turn confer risk for poor adjustment [98].

3.6.4 Stigma

Social stigma can influence illness-related adjustment when a person with a chronic disease perceives and/or internalizes negative societal attitudes toward their disease. Broadly, stigma is associated with adverse mental and physical health outcomes in the general population (for meta-analyses [99, 100]). Lung cancer survivors report frequent experiences of perceived stigma and high levels of internalized stigma [101, 102], which is linked to the perception that lung cancer via smoking behavior is a self-inflicted disease [103]. Lung cancer patients are more likely to blame themselves for their cancer and endorse personal causal attributions about their illness (e.g., beliefs that one's past behavior, such as smoking, caused the cancer), compared to breast and prostate cancer survivors; furthermore, stigma is more strongly related to psychological distress among lung, compared to breast or prostate, cancer survivors [104]. Stigma may confer risk for poor adjustment by prompting feelings of blame or regret [105], hindering health care utilization [106], and interfering with medical adherence [107]. Additional research should consider how cultural beliefs influence the experience of

stigma associated with cancer [108] and investigate how stigma longitudinally predicts psychological and physical adjustment following treatment completion in order to inform supportive care efforts that alleviate stigma and promote favorable adjustment to cancer.

3.7 Intrapersonal Influences on Adjustment

Several dispositional factors are influential in adjustment to cancer. Individual difference factors (e.g., personality attributes), the ways in which individuals cope with stressors, and spiritual or religious beliefs have important roles in psychological and physical adjustment. In the following section, three major psychosocial factors including: (1) personality attributes (i.e., neuroticism, optimism), (2) major domains of coping strategies (i.e., approach-oriented, avoidance-oriented), and (3) spirituality/religion are discussed. Each area is supported by evidence related to short and longer-term adjustment to the diagnosis and/or treatment of cancer.

3.7.1 Neuroticism

Neuroticism, the tendency to worry and experience negative affect, is associated with depression and distress in the general population [109, 110]. Neuroticism is also related to poorer quality of life, anxiety, and depressive symptoms among breast, lung, prostate, and colorectal cancer patients [111, 112]. Relationships between neuroticism and cancer-related physical morbidity also are apparent in long-term cancer survivors [113]. Several studies indicate that neuroticism may function as a vulnerability factor lowering the threshold for the development of depression following a cancer diagnosis [114]. A notable longitudinal study demonstrated that higher neuroticism at biopsy predicted greater psychological distress 2 years later among breast cancer survivors [115]. Although presumed relatively stable, neuroticism can in fact change over time following cancer treatment completion [116], and psychosocial interventions that address cancer-related anxiety or fear of recurrence [117] may be beneficial for reducing the impact of neuroticism on psychological maladjustment.

3.7.2 Optimism

Optimism is defined as holding a generalized view that positive outcomes are likely and is consistently associated with positive physical and psychological health in adults with or without cancer [49, 118–120]. Optimism at the time of cancer diagnosis prospectively predicts decreased distress and improved quality of life up to 1 year later [121, 122]. Optimism also longitudinally predicts better cognitive functioning, less pain, and better quality of life for head and neck cancer survivors 3 months following treatment completion [123] as well as less distress among early-stage breast cancer survivors across 12 months after treatment completion [124].

Optimism theoretically and empirically is positively related to adaptive, approach-oriented coping strategies and negatively related to avoidance [125]. Higher perceived emotional social support [124] as well as greater use of approach-oriented coping strategies (e.g., active acceptance; [121]) and lower use of avoidance-oriented coping (e.g., behavioral disengagement [121]) have been shown to explain, in part, the relationship between optimism and distress in breast cancer survivors. Research also indicates that individuals high in optimism evidence coping flexibility, or the ability to adjust coping efforts based on the actual demands of the stressor. Optimism may also be related to asking for help from others and drawing on available social support [126].

The physiological mechanisms of optimism continue to be investigated. Some studies indicate that greater optimism is related to compromised immune function in the face of uncontrollable stress and is associated with more competent immune function when stressors are controllable and brief [127]. In the case of

uncontrollable stress, greater optimism may be related to compromised physiological functioning because an optimistic, positive expectation is not realized, which then prompts feelings of disappointment [127]. In addition to studies of how optimism influences psychological and physical health, more research is needed to identify for whom and under what conditions optimism predicts favorable adjustment.

3.7.3 Approach-Oriented Coping

Stress and coping theory posits that adjusting to stressful experiences involves appraisal processes and coping efforts [128]. Broadly, coping can be categorized into the domains of approach-oriented and avoidance-oriented processes [129]. Approach-oriented coping entails efforts to directly confront or deal with the stressor and/or stressor-related emotions and includes such strategies as problem solving, positive reappraisal, cognitive processing, active acceptance, emotional processing, and emotional expression [130, 131].

Approach-oriented coping is generally related to favorable adjustment to cancer [132, 133]. For example, cancer-related active acceptance and positive reinterpretation (e.g., trying to grow as a result of or learning something from the cancer experience) predicted better psychological adjustment across 1 year following surgical treatment for breast cancer [134]. A longitudinal study of prostate cancer patients demonstrated that emotional expression prior to surgery facilitated cognitive processing of the stressor, which in turn predicted favorable psychological adjustment following treatment completion [135]. Processing and expressing emotions (i.e., coping through emotional approach; [136]) longitudinally predicts increased vigor and post-traumatic growth as well as declining distress among post-treatment breast cancer survivors [137]. Of note, among male cancer survivors, emotionally expressive coping was related to poorer adjustment in those with social constraints [138], indicating that the social context and individual difference factors influence the adaptive effects of coping strategies on adjustment [139]. Greater use of approach-oriented coping strategies likely promotes positive adjustment through both intrapersonal and interpersonal processes. Specifically, approach-oriented coping strategies are theorized to facilitate goal engagement [140], allow for prolonged exposure to the stressor [141] which over time can attenuate negative emotional responses, and promote recruitment of social support resources [142].

3.7.4 Avoidance-Oriented Coping

Efforts to disengage and escape from a major life-threatening stressor or its related emotions are considered to be avoidance-coping strategies (e.g., denial, coping through substance use, behavioral and mental disengagement). Cross-sectional and longitudinal research provides robust evidence that coping through avoidance predicts poorer adjustment to cancer [49, 132, 133, 143]. Most studies to date, however, investigate the relationships of avoidance with adjustment during active treatment or among newly diagnosed patients [144–146]. In a study of longer-term breast cancer survivors, avoidance-oriented coping at 6 months post-treatment longitudinally predicted poorer psychological adjustment 3 years later [147]. Coping through avoidance may contribute to poor physical and psychological adjustment through nonadherence to prescribed regimens, delay in seeking medical attention for physical symptoms, and increased frequency of cancer-related intrusive thoughts [145, 148].

3.7.5 Spirituality and Religious Beliefs

Following cancer diagnosis and treatment, many adults report finding strength in their spiritual or religious beliefs. Researchers have distinguished between existential (e.g., meaning and purpose in life, sense of peace) and religious (e.g., faith in a higher power) aspects of spirituality [149]. Overall, higher levels of spirituality are associated

with better psychological and physical health outcomes for cancer patients [49, 150, 151]. Studies have consistently found that facets of existential spirituality, compared to faith and religious spirituality, are more robustly linked to positive adjustment among breast [53], colorectal [152], and mixed cancer survivor samples [149]. Furthermore, one study of cancer survivors after treatment demonstrated that the relationship between higher religiosity and better quality of life was fully explained by a sense of meaning and purpose in life [149].

Cancer survivors with a greater sense of meaning and purpose in life may be more optimistic and use approach-oriented coping strategies such as active acceptance, which may in turn promote positive adjustment. Additionally, stronger religious beliefs may be associated with social support from one's faith-based community as well as active acceptance, which may facilitate favorable adjustment. Few studies have investigated whether intrapersonal and interpersonal factors predict changes in spirituality or the links of spirituality with associated appraisals and coping behaviors. Such investigations would be important for identifying modifiable psychosocial factors that could be harnessed through intervention to promote health and well-being via spiritual pathways. In some cases, it may be beneficial for medical providers to provide a referral to spiritual counselors to help cancer survivors address existential concerns.

3.8 Enhancing Adjustment Among Survivors

Numerous randomized controlled trials (RCTs) of psychosocial interventions have been conducted for people living with cancer. Multiple intervention approaches have been tested, including cognitive-behavioral therapy (CBT; [153]), mindfulness-based interventions [154, 155], relaxation training [156], psychoeducation [157–159], coping skills training [43, 160], and couples counseling [161]. There is considerable variability in the types of outcome variables examined within each trial, including psychological, physical, behavioral, physiological, and disease outcomes. Reviews of the literature indicate that psychosocial interventions are generally more effective when trial participants are selected because they surpassed a threshold for severity on the outcome of interest [162, 163]. Although information on these interventions is covered elsewhere in this textbook, it is important to note that much of the research focused on promoting adjustment to cancer survivors is dedicated to those in the early survivorship phase. There is a wide array of evidence-based psychosocial interventions (e.g., Cognitive Behavioral Stress Management; [164]) for promoting health and well-being for cancer survivors during and immediately after treatment.

In contrast, few interventions target cancer survivors who are several years beyond treatment completion. One such trial focused on reducing uncertainty and fear about cancer recurrence among breast cancer survivors who were between 5 and 9 years post-treatment completion [160]. Findings indicated that the intervention, relative to a standard care control condition, improved coping skills (e.g., cognitive reframing), which are theorized to reduce fear of recurrence. RCTs that target fear of dying [117] or recurrence [165] among long-term survivors are gaining attention; however, additional theoretically-grounded interventions are needed to target the needs of long-term survivors. Further, few psychosocial interventions are delivered to adults contending with poor-prognosis cancers (e.g., lung cancer, pancreatic cancer), and interventions for colorectal cancer patients largely produce small or null effects on health outcomes [166]. It is essential to maximize the effectiveness of psychosocial interventions to promote health and well-being among underserved and understudied groups.

Strikingly, relatively few psychosocial interventions for cancer survivors directly test mechanisms of change, which are important to understand in order to enhance the effectiveness of existing and future interventions. A review of the literature indicated four classes of mediators of effects of interventions for cancer survivors: (1) altered cognitions (e.g., expectancies), (2) self-efficacy for using skills that were taught by

the intervention, (3) protective psychosocial factors (e.g., self-esteem), and (4) cancer-related psychological and physical symptoms [167]. Future psychosocial interventions that target these mechanisms may be most beneficial for long-term cancer survivors' health and well-being.

3.9 Future Directions

As advances in medical treatment continue, research is essential for understanding and enhancing quality of life following treatment completion, and evidence-based supportive care is needed to maximize health and well-being for this growing population. Supportive care needs assessment can aid in identifying the concerns of cancer survivors; as such, it is important for oncology teams to prospectively screen for depression and anxiety [168] and assess needs, including those in the psychological and health information domains [169]. Additionally, oncology practices can offer routine distress screenings [170], and medical care teams can include mental health professionals (e.g., psychologists, clinical social workers) to reduce distress and promote well-being. Importantly, some cancer survivors benefit from ongoing support after oncologic treatment completion [171]. Accordingly, supportive care services should be offered to survivors at multiple points of the cancer care trajectory, including long-term survivorship.

Although improving recently, prior research on cancer survivorship has been conducted primarily with non-Latina white, highly educated early-stage breast and prostate cancer patients. Dedicated research that aims to understand health and quality of life as well as their predictors for historically marginalized populations (e.g., racial/ethnic minorities) remains a priority [172, 173]. Hispanic and African-American, compared to non-Hispanic white, long-term cancer survivors evidence more clinical and behavioral risk factors for morbidity [174], and the psychosocial needs of racial/ethnic minority, long-term cancer survivors are unknown. More research is needed to assess and address the distinct needs of racial/ethnic minority cancer survivors, and primary care physicians and oncologic medical teams should work collaboratively to deliver coordinated care [6, 175] that addresses behavioral and psychological health to promote positive adjustment for underserved cancer survivors.

Examination is warranted of the mechanisms through which the factors of race, ethnicity, age, SES, and gender are related to adjustment, beyond solely identifying group differences. In future research, psychosocial (e.g., gender roles) and environmental factors (e.g., health care access) should be measured and tested as explanatory factors for differences in adjustment as a function of race, ethnicity, age, SES, and gender. Additionally, supportive care efforts may be maximally effective when tailored to survivors' needs, which may vary significantly as a function of these psychosocial and environmental factors.

Cancer detection rates are improving, oncologic treatments for some cancers are advancing [176], and the American population is aging [177]. These factors contribute to the substantial projected increase in the number of adults living with a history of cancer. Continued research is warranted to represent the heterogeneous nature of the experience of survivorship, interrogate contributors to favorable outcomes during the reentry phase and beyond, and develop and disseminate effective interventions. Particular attention is needed to under-represented groups, survivors diagnosed with traditionally understudied cancers (e.g., lung cancer, pancreatic cancer), and those aged 65 years or older contending with multiple comorbidities [6]. An IOM report [178] detailed a number of existing psychosocial resources for cancer survivors, but emphasized the widespread lack of attention to survivors' needs and the failure of oncology teams to provide referrals to effective resources. Referral and access to evidence-supported resources is vitally important for cancer survivors across the entire cancer trajectory.

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Quality Care

4

Jonathan Sussman, Eva Grunfeld, and Craig C. Earle

4.1 Introduction

Since the publication of the landmark Institute of Medicine (IOM) report in 2005, cancer survivorship has been increasingly recognized as "a distinct phase of cancer care" [1]. Until that time, cancer survivorship had been relatively neglected in clinical practice, advocacy, and research. By virtue of their sheer numbers and the expected rate of growth of this population, estimated to be over 20 million by 2062 [2], the quality of the medical care cancer survivors receive is an increasingly important public health issue.

The IOM report set the stage to address this gap by defining and highlighting a constellation of long-term and late effects that result from having cancer treatment, issues around surveillance for and prevention of recurrence and second cancers, long-term and late effects of treatment, psychological sequelae, and social concerns regarding employment and health insurance. For the purposes of this chapter, we will limit the discussion to those aspects of care relevant to the patient who has completed primary therapy for cancer and is free of disease, no matter how soon after completion of treatment.

The specific problems survivors encounter may vary widely from person to person. It has been estimated that the average number of comorbid conditions among cancer survivors is five [3]. As a result, it is challenging 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. This 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 4.1). Though now over a decade old, the IOM report recommendations remain relevant to the provision of quality cancer survivorship care.

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Table 4.1 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 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)

4.2 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 key aspects of the patient's diagnosis, treatments received, and plan going forward. The goal is to optimize both the continuity and coordination of care. With the increasing complexity of cancer treatments, patients generally require treatment from multiple providers: surgeons, medical oncologists, radiation oncologists, nutritionists, and psychosocial providers, who may 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 the underuse and overuse of services.

Advocacy organizations, such as the American Cancer Society and the LIVESTRONG Foundation, have tried to empower survivors by providing information on survivorship issues for common cancer types and helping survivors summarize their medical treatment and plan for follow-up care [4]. The IOM recommended that it is incumbent on health-care providers, however, to become more proactive in assisting patients making the transition from cancer patient to cancer survivor.

To address the inconsistencies 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. Since the publication of the IOM report, there have been increasing efforts to define and operationalize the implementation of survivorship care plans. The idea of a formal, written plan has been generally accepted as an important facilitator of smooth transitions. While having face validity, research studies have not found the expected improvements in survivorship experience suggesting that more work is needed in the development and implementation of care plans [5, 6].

Despite these potential limitations, the Commission on Cancer (a program of the American College of Surgeons (ACoS) recognizes cancer care programs for their commitment to providing comprehensive, high-quality, and multidisciplinary patient-centered care) has added the use of care plans as part of a patient-centered approach to survivorship as a program accreditation standard for cancer centers in the United States [7]. Implementation has been challenging, as practical barriers to the creation of such document are significant. These are dis-

cussed 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.

4.3 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 [8].

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. Radiation oncologists will also often provide a summary of anatomical area treated and the dose of radiation given.

Medical oncologists do not consistently summarize a course of their treatment. 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 "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, any surgeries performed, the name of the regimen and component drugs, and starting dosages. It may also 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. In certain cancers, extended adjuvant treatment with endocrine therapy and similar summaries of radiation treatment that expand on location, dose, and fractionation (number of treatments that the dose was given over) should be given. Awareness of these elements of the patient's history is necessary to guide surveillance for recurrence and late effects.

4.4 Ongoing or Follow-Up 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. 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 and noncancer 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 does not 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. It may need revision as new knowledge about late effects (e.g., recognition of stroke as a complication of chemotherapy), 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) comes to light [9, 10].

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.

4.5 Guidelines for Survivorship Care

Ideally, the survivorship care plan would be organized around a set of widely agreed-upon clinical practice guidelines that outline aspects of survivorship care beyond surveillance for cancer recurrence. Guidelines are best when they are based on evidence and derived in a formal process of either evidence evaluation or consensus. There has been an increase in the number of comprehensive guidelines available for the management of cancer survivors. As an example, the American Society of Clinical Society has a separate web-based resource specific to survivorship care with topics that include surveillance as well as management of long-term toxicities [11].

Most guidelines continue to focus only on issues of surveillance [9, 10, 11, 12, 13]. Consequently, the third recommendation of the IOM report highlighted the need for the refinement of existing clinical practice guidelines to include survivorship care and included 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; clinical practice guidelines can decrease variation in care, particularly the overuse of investigations 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, and colorectal surveillance guidelines caution against the overuse of nonspecific blood work [10, 11, 15]. 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 [14, 17]. Indeed, randomized trials have not been able to consistently find positive psychological effects associated with surveillance [15, 18].

While being told that there is no sign of cancer recurrence can understandably decrease anxiety, 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 [18–21]. False-positive results cause mental distress and usually lead to further tests, possibly invasive ones such as a biopsy, that add expense and can lead to other complications.

Although 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.

4.5.1 Surveillance for Cancer Recurrence

Surveillance for recurrence of cancer is usually the first issue that comes to mind when survivor care is discussed. However, assessing the quality of surveillance care is not easy. Surveillance is something that appears to be an undeniable good thing. Patients like the notion of surveillance because after completing a regimented treatment program, many are reassured by the ongoing tasks (i.e., clinical examinations, laboratory tests, and/or imaging) of surveillance and resultant contact with their providers [18]. Oncologists also like the opportunity to provide reassurance [22].

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, and imaging studies.

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 [23].

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 [24]. Moreover, early institution of palliative chemotherapy in asymptomatic patients does not appear to provide benefit in many situations [16, 25]. Detecting and preventing potentially catastrophic complications of recurrence like spinal cord compression and pathological fracture have 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 [26].

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 [27].

Surveillance involves upfront costs for a future, uncertain benefit. These costs can be quite substantial. A previous estimate of average 5-year costs across all cancers was $14,534 in 1996 in US dollars [25]. 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 [29, 30].

For example, the breast cancer guidelines (Table 4.2) are decidedly minimalist around surveillance testing because of evidence that intensive surveillance does not improve outcomes. The colorectal guidelines (Table 4.3) have recently become a bit more intensive following publication of meta-analyses that suggest a small benefit for strategies that include imaging [31].

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.

4.5.2 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 months to years 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 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 [32]. The challenge when following

Table 4.2 ASCO breast cancer surveillance guidelines

Recommendation	Level of evidence[a]
It is recommended that primary care clinicians:	
Recommendation 1.1: History and physical (a) Should individualize clinical follow-up care provided to breast cancer survivors based on age, specific diagnosis, and treatment protocol as recommended by the treating oncology team (b) Should make sure the patient receives a detailed cancer-related history and physical examination every 3–6 months for the first 3 years after primary therapy, every 6–12 months for the next 2 years, and annually thereafter by the treating oncology team	2A[b,c]
Recommendation 1.2: Screening the breast for local recurrence or a new primary breast cancer (a) Should refer women who have received a unilateral mastectomy for annual mammography on the intact breast and for those with lumpectomies an annual mammography of both breasts (b) *Should not* refer for routine screening with MRI of the breast unless the patient meets high risk criteria for increased breast cancer surveillance as per ACS guidelines	2A[b,c]
Recommendation 1.3: Laboratory tests and imaging *Should not* offer routine laboratory tests or imaging, except mammography if indicated, for the detection of disease recurrence in the absence of symptoms	2A[b,c]
Recommendation 1.4: Signs of recurrence Should educate and counsel all women about the signs and symptoms of local or regional recurrence	2A[b,c]
Recommendation 1.5: Risk evaluation and genetic counseling (a) Should assess your patient's cancer family history (b) Should offer genetic counseling if potential hereditary risk factors are suspected (e.g., women with a strong family history of cancer [breast, colon, endometrial], or age 60 years or younger with triple- negative breast cancer)	2A[bc]
Recommendation 1.6: Endocrine treatment impacts, symptom management Should counsel patients to adhere to adjuvant endocrine (antiestrogen) therapy	2A[b,c]

Source: Guideline for Surveillance for Breast Cancer Recurrence and Genetic Counseling ASCO breast cancer follow-up guidelines table. C. Runowicz [14, 28]

Abbreviations: *ACS* American Cancer Society, *MRI* magnetic resonance imaging

[a]Levels of evidence: I indicates meta-analyses of randomized controlled trials (RCTs); IA, RCT of breast cancer survivors; IB, RCT based on cancer survivors across multiple sites; IC, RCT not based on cancer survivors but on general population experiencing a specific long-term or late effect (e.g., managing fatigue, lymphedema, etc.); IIA, nonrandomized controlled trial (non-RCT) based on breast cancer survivors; IIB, non-RCT based on cancer survivors across multiple sites; IIC, non-RCT not based on cancer survivors but on general population experiencing a specific long-term or late effect (e.g., managing urinary incontinence, erectile dysfunction, etc.); III, case-control or prospective cohort study; 0, expert opinion, observation, clinical practice, literature review, or pilot study

[b]National Comprehensive Cancer Network category 2A indicates that "based upon lower-level evidence, there is uniform consensus that the intervention is appropriate." Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, V.2.2015. ©National Comprehensive Cancer Network, Inc. 2015. All rights reserved. Accessed August 3, 2015. To view the most recent and complete version of the guideline, go online to NCCN.org. National Comprehensive Cancer Network, NCCN, NCCN Guidelines®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc.

[c]Referenced with permission from the American Society of Clinical Oncology (ASCO)

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 the population, are aging and have other comorbid conditions. Consequently, it may be difficult to determine whether relatively vague complaints like fatigue or cognitive limitations need to be aggressively worked up as a possible harbinger of a cancer recurrence or late effect of cancer treatment or managed as it would be in a patient without a history of cancer.

Table 4.3 ASCO colorectal cancer surveillance guidelines

Procedure	Timing	Additional notes
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	
Computed tomography (CT) of the chest and abdomen	Annually for 3 years	Pelvic CT scan for rectal cancer surveillance
Colonoscopy	Three years after operative treatment	If results are normal, every 5 years thereafter
Flexible proctosigmoidoscopy	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	Not recommended	
Molecular or cellular markers	Should not influence the surveillance strategy based on available evidence	

Source: Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement. Meyerhardt et al. [10]

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.). Quality cancer survivorship care must include an assessment, recognition, and management of these effects. Table 4.4 lists some selected common late effects.

4.6 Surgery

4.6.1 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 it up with their care providers. 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.

4.6.2 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 in order to optimize their function and activity.

4.6.3 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 [33]. However, in the post-thoracotomy pain syndrome, the discomfort can be constant and disabling. It is felt to be possibly

Table 4.4 Common long-term and late effects of cancer treatment surgery radiation systemic therapy

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

due to scar tissue involving the intercostal nerves that run along the ribs [34]. 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 [35]. Post-thoracotomy pain can often require oral analgesics and in refractory cases nerve blocks and epidural anesthetic pumps.

4.6.4 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, minorities 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 [36].

4.6.5 Pelvic Surgery

Bladder and bowel dysfunction can greatly affect patients' quality of life [37]. 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 oxybutynin or tolterodine can be helpful, but some patients need further surgical intervention such as the implantation of prosthetic urethral sphincters [38]. Damage to the autonomic nerves, such as during

a prostatectomy, can also cause erectile dysfunction which may require pharmacologic or surgical management.

4.6.6 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 [39]. 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 routinely 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 the 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.

4.6.7 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.

4.7 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. Recent advances in the planning and delivery of radiation in a more precise and targeted manner are expected to result in fewer late complications, but long-term follow-up is required to confirm that this is the case. For example, in head and neck cancer, the use of intensity-modulated radiation to spare salivary gland function is expected to result in less dryness of the mouth and dental complications in patients receiving high-dose treatment to these areas [40].

4.7.1 Second Malignancies

Second cancers now account for over 15% of the incident cases of cancer [41]. 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 who 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 [42]. Abdominal radiation is also associated with gastrointestinal malignancies.

Rectal cancer is more common after radiation for prostate cancer [43]. Myelodysplasia and acute leukemia can also develop after radiation [44]. 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.

4.7.2 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 [45]. 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 the use of notes to aid memory.

The eyes and their surrounding structures may be exposed 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.

4.7.3 Chest Radiation

Chest irradiation can damage any of the structures in the chest. For example, breast irradiation can in some cases interfere with lactation [46]. 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 [47]. 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 [48].

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 [49]. Patients who had radiation for a left-sided breast cancer using older techniques are at higher risk of cardiac mortality than those with right-sided breast cancer [50, 51]. 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, and abdominal radiation can lead to renovascular hypertension [52]. Newer techniques designed to minimize these effects have decreased the risk for patients in recent years [53]. In addition to being aware of these problems, optimization of modifiable risk factors such as smoking and lipid levels should be encouraged.

4.7.4 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.

4.7.5 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 [54]. 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 [55]. Medications for urge incontinence like oxybutynin or tolterodine may be helpful [56]. 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 ovariopexy (surgically moving the ovaries out of the radiation field) is performed, likely due to the scatter of radiation outside of the intended field [57]. Unfortunately, there is often insufficient time to stimulate and harvest ova prior to therapy. Radiation doses to the ovaries as low as 20 Gy induce premature menopause in women under 40 years, and as little as 6 Gy will induce ovarian failure in women between 40 and 50 years [58].

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 [59]. 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 [60]. 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 [61]. Referral to a urologist specializing in male sexual health can be very helpful.

4.7.6 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 the 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. An increased risk of hip fracture has also been recognized following pelvic radiation [62]. Providers must recognize that in these patients, osteopenia and osteoporosis may be focal, and if present, they

must consider interventions such as bisphosphonates and recommendations for weight-bearing and muscle-strengthening exercise.

4.7.7 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 [64]. It is dose dependent, increasing with doses above 25 Gy, and usually occurs within 2–3 years [65].

Much less frequently, cranial irradiation to doses above 50 Gy can affect the hypothalamus and pituitary leading to central hypothyroidism [65, 66]. 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 [67].

4.8 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.

4.8.1 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 electrophilic alkyl group with an affinity for the N7 position on guanine. As a result, it intercalates itself between DNA strands causing mispairing of nucleotides and single- and double-strand breaks.

Other drugs, such as the platinum, 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.

4.8.2 Cognitive Effects

"Chemo brain" is being increasingly recognized as a constellation of mild cognitive problems associated with prior exposure to multiagent chemotherapy [63]. 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, the specific mechanisms are unknown [68]. Moreover, it is not clear that chemotherapy itself causes these symptoms as detectable pretreatment impairment of cognition has been demonstrated in cancer patients [69]. 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.

4.8.3 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 that 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 [70]. 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 increased 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.

4.8.4 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 contraindication in patients with a history of breast cancer. Consequently, other treatments must be used for hot flashes, such as antidepressants [71]. 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 an adult cancer patient is, the more likely they are to have their fertility preserved after chemotherapy [72]. 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 no clear evidence that pregnancy increases the risk of relapse or that there is increased risk of birth defects in cancer survivors [73]. 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 [59, 74]. Among breast cancer survivors, sexual dysfunction appears to be more closely related to receipt of chemotherapy than the body image concerns resultant from mastectomy or tamoxifen effects although all may play a role [75–79]. Many of these symptoms improve with prolonged (i.e., >5 years) follow-up [80].

4.8.5 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 the bone. They are also associated with avascular necrosis. Lastly, hormonal treatments for breast and prostate cancer accelerate bone loss, osteoporosis, and fractures [81]. The endocrinology is complex, however. Tamoxifen can preserve bone mineral density in postmenopausal women but is associated with bone loss in younger women [82]. Aromatase inhibitors adversely affect bone density in all ages [83]. 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 [84]. Bisphosphonates can be useful for the treatment of osteoporosis.

4.8.6 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, and the acrolein metabolite of cyclophosphamide and ifosfamide causes a hemorrhagic cystitis that in a small proportion of patients can become chronic after a severe acute episode [85]. Cisplatin can affect renal function, which can be either acute or of delayed onset. Vinca alkaloids, 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 [86].

4.9 Psychosocial Concerns

The majority of the evidence suggests that cancer survivors have good emotional functioning after cancer although rates of some diagnoses, such as depression, are higher among cancer survivors than in the general population [87–89]. Fear of recurrence and death understandably dominates adjustment disorders and may reach the extent where they interfere with vocational and personal pursuits [90].

Cancer survivors with preexisting anxiety or affective disorders appear to be at greatest risk for ongoing distress [33]. Changes to body image from cancer therapy, such as that resulting from mastectomy or colostomy, can be a source of problems with psychological adjustment [91]. Distress appears to dissipate with time, however. There are a small proportion of patients who experience ongoing effects characteristic of posttraumatic stress disorder [92]. Having a spouse or partner decreases the risk of psychological sequelae although these caregivers may also themselves be adversely affected [93, 94]. Social networks and support groups have been found to improve mental health in breast and prostate cancer survivors [95, 96]. Cancer appears to cause a greater detriment to the quality of life of younger patients than the elderly likely due to the greater disconnect between their expectations for health, physical functioning, and roles at that stage of life than when older [97, 98].

A small proportion of cancer survivors report persistent fatigue at levels above population norms. Depression and chronic pain are commonly associated with these cases [99]. 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 [100, 101]. Sense of well-being has been reported to be better among cancer survivors than respondents without a history of cancer, and marital relationships may be strengthened [75, 89]. 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.

4.9.1 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, noncancer health care is equally as, and in many cases, more important than surveillance. Most patients diagnosed with cancer today are expected to survive it. Many studies have shown that potentially preventable conditions like heart disease and diabetes are actually the greatest threat to life for many of these patients [102, 103]. 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" [104]. 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, 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 [105, 106]. A blinding focus on the prior malignancy, nihilism about the prognosis, or simply loss to follow-up with primary care providers 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 [105, 106]. Patients followed exclusively by primary care physicians might be 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 noncancer care. Patients followed by both types of physicians consistently appear to receive the highest-quality care. One explanation for these observations is that there may be a lack of clarity around the relative roles primary care and specialist physicians will play in a survivor's care [107]. Also, 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 [108]. 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.

4.9.2 Genetic Assessment

The transition from 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 also surveillance recommendations for the patient. For example, interval cancers are more common among patients with hereditary nonpolyposis colorectal cancer, and so surveillance colonoscopies should be more frequent.

4.9.3 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 suggests 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.

4.9.4 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 consider.

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 4.1 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 person 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 non-physician 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 providers 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.

4.10 Future Directions

Significant progress has been made in raising awareness of the issues facing cancer survivors. Organized programs and specific resources such as guidelines to address the unique challenges of cancer survivors have been developed in a number of jurisdictions, and evaluations are ongoing. This population has been clearly recognized as distinct with many 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 currently the most important aspects of high-quality survivorship care. Implementation of the principles articulated in the IOM recommendations continues to ensure that the transition along the cancer trajectory from patient to survivor can be as smooth as possible and that this growing population receives quality of care.

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 contrary" and call 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 4.5 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. 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

Table 4.5 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 treatment, surveillance, and late effects (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 policy 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 information technologies to support the use of medical records (smart cards, web-based data) for the increasingly mobile survivor population
Determining the cost-effectiveness of different survivorship care models and strategies

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 resources used. As survivorship programs continue to develop, measuring effectiveness by considering survivor, provider, and health system outcomes is essential to support optimal outcomes of care [109].

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Part II

Unique Challenges

Disparities

5

Denalee M. O'Malley, Jennifer Tsui, Stacy N. Davis, and Shawna V. Hudson

5.1 Introduction

Health disparity populations within the United States (USA) have been defined by the National Institute on Minority Health and Health Disparities as including racial/ethnic minorities; low socioeconomic status; rural, sexual, and gender minority; and groups with other fundamental characteristics (e.g., disability and geographic region). Factors that influence health disparities occur across a continuum of multi-level drivers including biological, behavioral, physical built, sociocultural environment and health systems. Cancer health disparities, as defined by the National Cancer Institute's Center to Reduce Cancer Health Disparities, are "adverse differences in cancer incidence (new cases), cancer prevalence (all existing cases), cancer death (mortality), cancer survivorship, and burden of cancer or related health conditions that exist among specific population groups in the United States" [1].

Over the past 10 years, we have seen increased interest in disparities in cancer survivorship. The American Society of Clinical Oncology's statement on achieving high-quality cancer survivorship care [2] describes the following limitations in cancer survivorship care as drivers of disparities: (1) lack of standardized models of care, (2) paucity of clinical guidance for survivors of various cancer types treated across the life span, and (3) barriers to access to high-quality survivorship care (e.g., lack of insurance, insurance restrictions). This report endorsed the need for investments in research to expand the evidence base to enhance the quality of cancer survivorship care provided in clinical practices [2, 3]. We have seen significant expansion in the knowledge base. It has moved beyond early epidemiological studies focused on elucidating Black-White differences in survival and impact of low socioeconomic status on survival. Now, the literature is informed by numerous studies that examine not only survival but also prevalence and the interface of factors that contribute to ongoing cancer survivorship disparities post-acute treatment for multiple groups (e.g., racial and ethnic minorities, low

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socioeconomic status, individuals with multi-morbidity, and sexual identity). This chapter describes the key research, healthcare, and policy findings related to the intersection of cancer health disparities and cancer survivorship care [4]. Further, the purpose of this chapter is to provide an overview of cancer survivorship disparities focused on key health disparity populations (i.e., racial and ethnic minorities, low socioeconomic status, individuals with multi-morbidity, and sexual identity) as well as the impact of limited access to continuous care and fragmented care systems on cancer survivorship disparities.

5.2 Overview of Disparities in Cancer Outcomes

5.2.1 African-Americans

Differences in cancer survival in the United States continue to persist between non-Hispanic Whites (NHW) and racial ethnic minorities [5, 6]. The burden of cancer has been disproportionately borne by African-Americans, a population with the highest mortality rates and shortest survival times for most cancers [7] compared to all racial and ethnic groups [6, 7]. The diversity of subgroups within the African-American population continues to be understudied despite recent reports that indicate that the demography has shifted with a growing immigrant population more prominent than in previous decades (e.g., 8.7% of the nation's Black population) [8]. Evidence supports that the greatest predictors of health disparities among African-Americans are social (e.g., education, structural racism, income disparities) rather than biological [4, 7]. Five year relative survival is lower among African American breast cancer patients when compared to NHW patients at each stage of diagnosis [5]. Compared to NHW American males, African-American males have 12% higher incidence rates for all cancers combined (e.g., prostate, lung, colorectal, kidney, and pancreas, Fig. 5.1), whereas African-American women are estimated to have a 6% lower incidence rate of all cancers combined compared to NHW American women [6].

Mortality rates for most cancers are higher among African-Americans than NHWs [6]. While the disparity gap has narrowed for most cancers among both men and women, for select cancers, the gap has widened or remained stable [6]. Specifically, the mortality rates for breast cancers have widened between African-American and NHW American women, while the rates have remained stable for colorectal cancer in African-American and NHW American men [6]. Given these trends, a continued emphasis on prevention, early detection, and access to high-quality treatment remains a promising avenue to address health disparities between African-Americans and NHW Americans [6]. Emerging survivorship studies of health service use and neighborhood contextual factors among African-American breast cancer survivors suggest that multilevel strategies that extend beyond the acute phase of care are warranted. One study found that adherence to routine follow-up guideline-recommended surveillance care (e.g., mammography and clinic visits) was poorer among African-American breast cancer survivors when compared to NHW survivors [9]. Further, in a study of ethnic minorities that included a large subsample of African-American survivors, greater neighborhood stress was found to be associated with poorer self-reported health, more comorbid illnesses, and more depressive and higher psychological difficulties [10]. Attending to the morbidity burden and sociocultural contextual factors during the post-acute treatment phase is an emerging area of study. Examining the impact of processes of care and context of care on African-American health disparities is needed, specifically those that extend this growing body of research into examination of other cancer sites.

5.2.2 Hispanic/Latino Americans

In the United States, the Hispanic/Latino population is a heterogeneous ethnic categorization that refers to individuals of Mexican, Cuban, Puerto Rican, South or Central American, Dominican, or

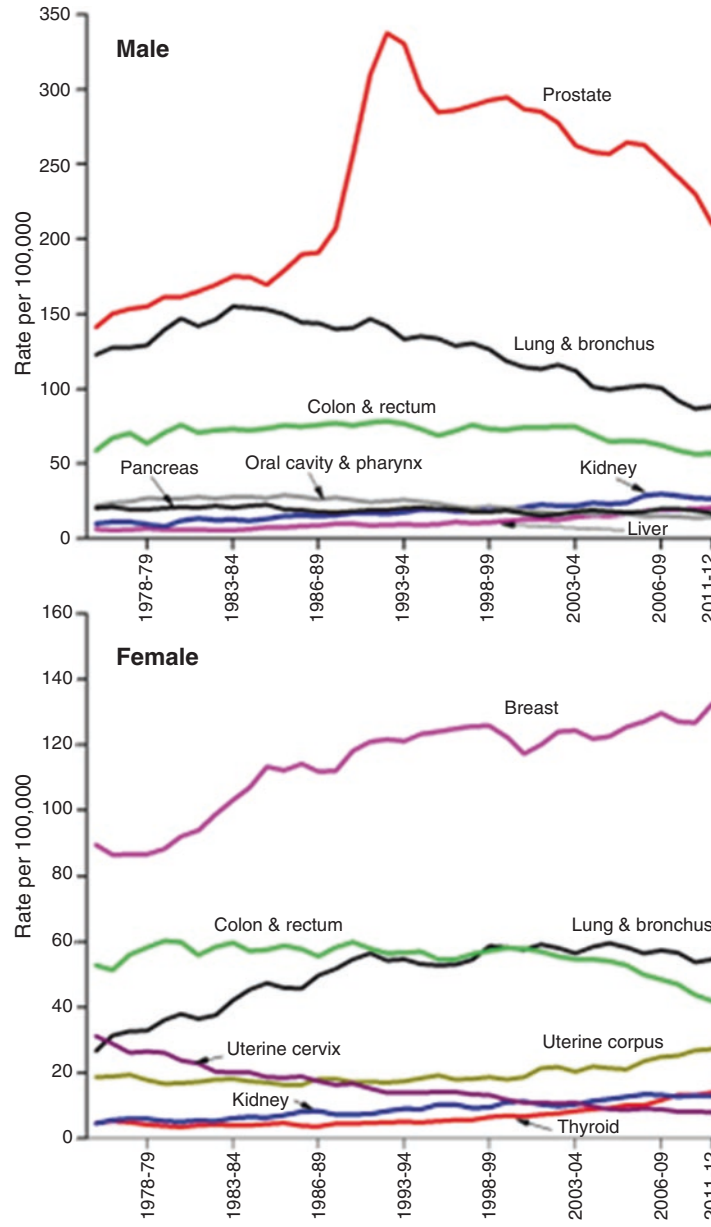

Fig. 5.1 Cancer statistics for African Americans, 2016: trends in cancer incidence rates among Blacks, United States, 1975 to 2012. (From DeSantis et al. [6]. http://onlinelibrary.wiley.com/doi/10.3322/caac.21340/full#caac21340-fig-0007)

other Spanish decent [11, 12]. Data have shown that while Hispanics have 20% lower cancer incidence rates and 30% lower mortality rates compared to NHW, mortality rates are higher for adolescent Hispanic cancer patients [12]. Hispanics have lower incidence rates across the most prevalent cancers in the U.S. (i.e., prostate, breast, lung, colorectal; see Fig. 5.2). Despite lower general cancer incidence rates among Hispanics, trends suggest that Hispanics are more likely to be diagnosed at later stages than NHWs. Further, Hispanic populations have higher incidence rates for specific cancers including acute lymphocytic leukemia, gallbladder cancer, and cancers associated with infectious diseases (e.g., stomach, liver, cervix, etc.) compared to rates among NHWs [12]. Liver cancer incidence and mortality rates remain consistently elevated among Hispanics compared to NHWs, with Hispanic men being twice as likely to have liver

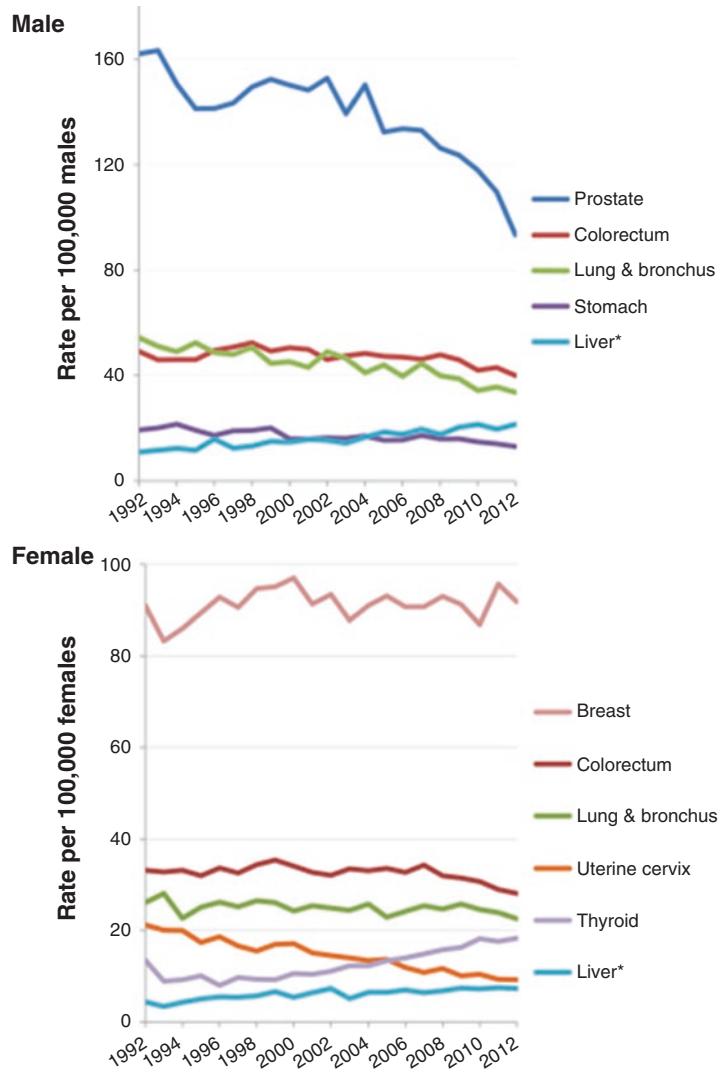

Fig. 5.2 Cancer statistics for Hispanics/Latinos, 2015: trends in cancer incidence rates among Hispanics, United States, 1992 to 2012. (From Siegel et al. [12]. http://onlinelibrary.wiley.com/doi/10.3322/caac.21314/full#caac21314-fig-0002)

cancer than NHW men [11, 12]. Overall variations in cancer incidence between Hispanics and NHWs are hypothesized to be the result of both social contextual issues (e.g., nativity, environmental exposure to carcinogens) and behaviors that elevate cancer risk rates (e.g., obesity and diabetes) [13, 14].

Among Hispanic breast cancer survivors, many known factors have been shown to be associated with poorer outcomes (e.g., clinic visits, follow-up mammography) and less frequently adhered to among Hispanic survivors when compared to NHW survivors [9]. Results from a study designed to model health-related quality of life among racial/ethnic minority breast cancer survivors with a large sample of Hispanic survivors suggest that sociocultural context (ethnicity, life stress, social support) explained 20% of the variance, demonstrating a larger influence than health status and behavioral factors (18%), demographic factors (14%), and health system factors (8%) [15]. Wu and colleagues suggest that an emphasis on the contextual impacts on health-related quality of life, specifically the impact of greater neighborhood stress on poorer health-related quality of life among ethnic minority (e.g., NHW) breast cancer survivors, is needed [10].

5.2.3 Asian-Americans, Native Hawaiians, and Pacific Islanders

The US Asian-American/Pacific Islander population is also a heterogeneous categorization describing a diverse subpopulation that includes Asian-Americans (e.g., Asian Indians, Cambodians, Chinese, Filipinos, Hmong, Japanese, Koreans, Pakistanis, Vietnamese, etc.), Native Hawaiians, and Pacific Islanders (e.g., Chamorros, Fijians, Samoans, etc.) (AANHPIs) [16]. Incidence data have consistently documented that while AANHPIs experience lower rates of cancer overall, the highest incidence rates within AANHPIs are attributed to breast, prostate, colorectal, and lung cancers (see Fig. 5.3). Additionally, AANHPIs have a disproportionately higher risk of developing cancers of infectious origins (e.g., hepatitis C, HPV) when compared to NHWs [16]. Cancer rates and risk vary widely among AANHPI subpopulations; therefore, cancer prevention, control, and survivorship strategies may benefit from considering these subpopulation differences [17, 18].

A mixed method study qualitatively described socioeconomic well-being (SWB) as a concern among US-born Chinese, immigrant Chinese, and NHW survivors [19]. The quantitative findings suggest Chinese immigrant survivors report the lowest SWB; however, across the study sample, women with lower incomes and recipients of chemotherapy reported low SWB. Generally, highly acculturated immigrant Chinese, US-born Chinese, and NHW survivors reported similar levels of SWB. More research is needed to develop knowledge about the complex cultural factors and contextual barriers specific to subpopulations of AANHPI in efforts to develop targeted and responsive interventions.

5.2.4 Native American/American Indian and Alaskan Natives

In the past two decades, American Indian and Alaskan native (AI/AN) populations benefitted less from progress to improve cancer mortality when compared to NHWs [20]. The presence of wider health disparities among AI/AN is demonstrated when geographical variations in mortality and incidence are considered [20]. These differences were in part attributed to contextual variation in lifestyle behaviors (e.g., cancer screening, tobacco use, obesity, etc.) [21]. Quality-of-life outcomes comparing AI/AN cancer survivors to non-AI/AN survivors found that AI/AN reported lower physical and social QOL, similar psychological QOL, and higher spiritual QOL [22].

Community-based participatory research projects such as the Native Navigators and the Cancer Continuum have shown promising results to engage community members and improve access to services among newly diagnosed and in building awareness about cancer-related resources [23]. Using a community-tailored approach, this investigation demonstrates the receptivity across AI/AN groups to build capacity toward improvements in cancer care. Explorations about how these efforts might influence different domains of cancer survivorship are needed [23].

5.2.5 Sexual Minorities

A 2011 Institute of Medicine report described the current lack of research regarding the health experiences of sexual minority populations, with gaps in the cancer literature spanning the cancer control continuum from prevention to survivorship [24]. Due to the lack of cancer surveillance data on sexual minorities, population-level data to assess incidence and risk factors specific to this population are lacking across the cancer continuum [25]. In a regional study conducted by Boehmer et al. [26], no significant difference in cancer prevalence among women by sexual orientation was reported. However, this study found lesbian and bisexual females had 1.0 and 2.3 greater odds of reporting poor or fair health compared to heterosexual female survivors. In contrast, men who have sex with men (MSM) had 1.9 greater odds of reporting a cancer diagnosis compared to heterosexual men [26]; however, no relationship between sexual orientation and self-reported health (e.g., ratings of health from

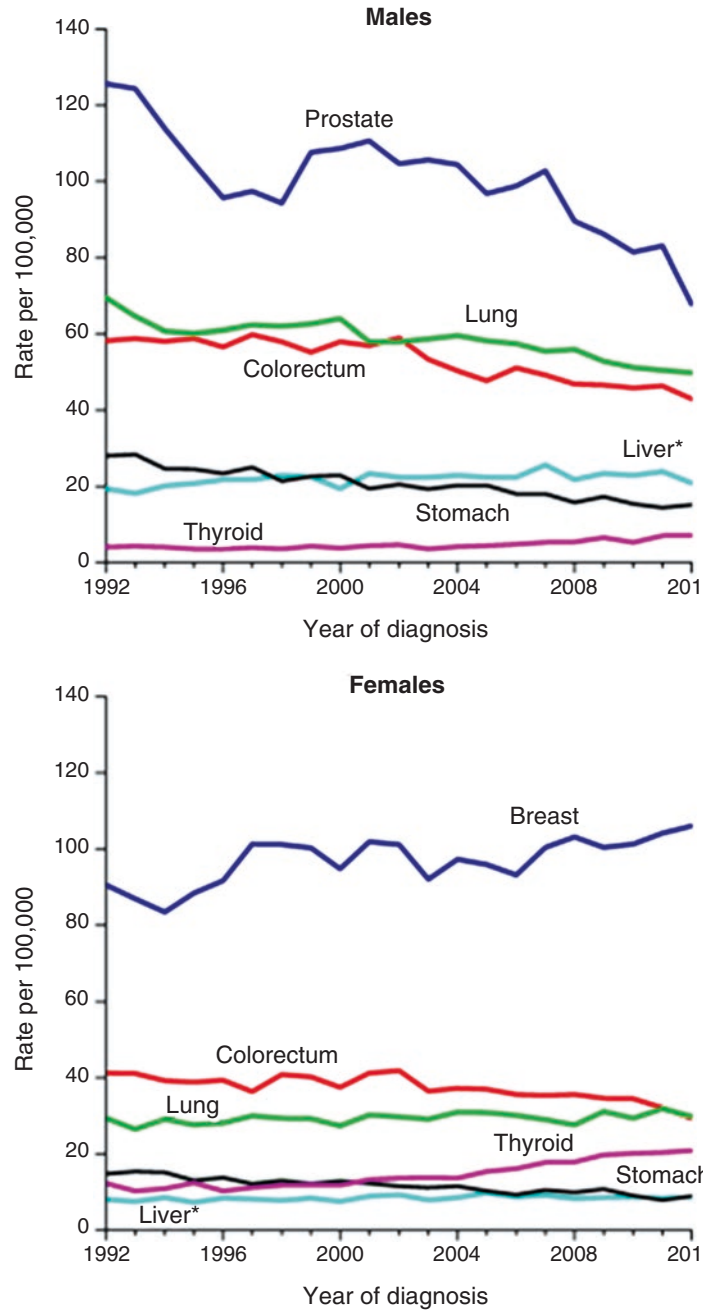

Fig. 5.3 Cancer statistics for Asian/Pacific Islanders 2015: trends in cancer incidence rates among Asian Americans, Native Hawaiians, and Pacific Islanders, United States, 1992 to 2012. (From Torre et al. [16]. http://onlinelibrary.wiley.com/doi/10.3322/caac.21335/full#caac21335-fig-0006)

excellent to poor) status was found among men. Studies have found no differences in quality of life between heterosexual, lesbian, and bisexual women [27, 28]; however, sexual minority women have been shown to have greater post-breast cancer treatment morbidity and systemic side effects [29]. Survivorship research for less common cancer sites that impact women (e.g., cervical cancer) have been less well studied among sexual minority women [30]. Among MSM, higher prevalence for specific cancers has been attributed to sexually transmitted diseases

that are also more prevalent in the MSM population. Studies suggest that elevated rates of human papillomavirus (HPV) in MSM contribute to elevated risk for head and neck cancers [31] and anal cancers [32]. Further, documented human immunodeficiency virus (HIV) infection is associated with elevated rates of Kaposi's sarcoma, anal cancers, non-Hodgkin lymphoma, liver cancer, and lung cancer [29, 30, 33].

Population-based research that explores relationships between sexual minority status and cancer outcomes is limited overall; however, research within the transgendered population is particularly inadequate [34]. Among the transgendered population, conflicting evidence has been presented regarding the risk of breast cancer incidence [35, 36]. Case studies suggest the need to explore further cancer-specific risks related to the use of both masculinizing and feminizing hormones [24]. Additionally, evidence-based interventions are needed to inform nonjudgmental and knowledgeable approaches to long-term survivorship effects that specifically impact subpopulations of sexual minority survivors. For example, MSM posttreatment for anal cancers may endure long-term sequelae that present specific challenges to future intimacy, including sexual impairment and relationship adjustment to accommodate changes in functioning [30, 37]. Cultural competency training among health providers and the development of evidence to inform subpopulation-specific assessment and interventions have the potential to enhance quality of care [32, 40].

A major challenge to the provision of evidence-based care is that survivorship concerns specific to sexual minority subpopulations have not been well studied. Barriers to healthcare delivery for this population include a history of both institutional discrimination and interpersonal stigma (e.g., heterosexism, transphobia, etc.) directed toward sexual minorities from health professionals [38]. Sexual minorities in many cases must choose to disclose their gender identity or sexual behaviors to their providers. Many of the consequences during survivorship are related to identity, relationships, and sexuality; therefore, an initial step to develop culturally sensitive assessment and intervention is fostering a safe environment for sexual minorities to disclose their gender identity and sexual behaviors to providers [39].

5.3 Implications of Disparities for Cancer Survivorship

Cancer survivorship is characterized by a long-term need to manage late- and long-term treatment effects. The impact of cancer treatment and its effect on cancer survivorship are differentially experienced by health disparity populations. This section explores the impacts of socioeconomic status, financial toxicity, and multi-morbidity on cancer survivorship health disparities.

5.3.1 Socioeconomic Status

The relationship between cancer and socioeconomic status (SES) is multifaceted and intersectional based on historical structural income inequalities among specific racial and ethnic subpopulations. Multiple factors including access to healthcare, screening utilization, behavioral risk, and occupational hazards strongly influence cancer incidence and are similarly associated with SES. Cancer incidence and mortality vary by SES in the United States [5, 6]. Low SES is associated with incidence and mortality rates for lung, colorectal, cervical [40], oral [41], and liver cancers [42].

Cancer incidence for other sites including breast, prostate, skin [40], and thyroid [38] are associated with higher SES [43]. In general, cancer incidence for sites that are associated with behavioral risk factors (i.e., tobacco use, alcohol, diet, intravenous drug use, and sexually transmitted infections) tends to be associated with lower SES [44]. Further research is needed to appreciate the impact of SES on QOL outcomes during cancer survivorship. Early insights regarding the breast cancer survivor population suggest that mental and physical health-related quality-of-life outcomes differed according to income, education, and job type, with survivors' belonging to higher

SES groups reporting better physical and mental health [45]. Additionally, these findings suggest that environmental stressors (i.e., housing situation, neighborhood, use of public services, violence exposure, and relations with the police) were the strongest predictor influencing physical and mental quality of life among breast cancer survivors [45].

5.3.2 Financial Toxicity

Across socioeconomic groups, financial toxicity (i.e., having high out-of-pocket costs that causes distress and impacts quality of life) post-acute treatment for cancer is now recognized as a major concern among survivors and has been found to be associated with higher mortality and distress [46]. This topic will be discussed briefly with a focus on disparity related to the cancer survivorship experience. A 2015 systematic review found that 16% to 78% of survivors experienced financial hardship as a result of their cancer [47].

A recent study found a consistent positive relationship between cancer survivors who declared bankruptcy and an increased risk of mortality (that varied in magnitude by cancer site) [48]. Racial and ethnic minority patients appear most vulnerable to financial decline attributable to breast cancer, even after adjustment for income, education, and employment [49]. Among insured individuals, a cancer diagnosis can prove financially catastrophic for patients and their families. Unfortunately, much of this research has focused on the impact of out-of-pocket costs among insured individuals and remains understudied among uninsured groups [50]. Financial toxicity as an adverse effect of cancer treatment can manifest as increased emotional and physical distress [46]. Financial toxicity has been found to be associated with poorer adherence to treatment [51] and poorer health-related quality of life among survivors in treatment and those with advance cancer [52]. Given that financial concerns have been shown to contribute to survivors foregoing medical care, additional explorations into how cost is a driver for health-related disparities are needed [53, 54].

5.3.3 Multi-morbidity

Approximately 25% of Americans have multimorbidity, defined as two or more concurrent chronic conditions that may include both physical (e.g., cardiovascular disease, diabetes, obesity, and cancer) and psychological conditions (e.g., depression and anxiety) [3], which may result in increased disability and impairment. Generally, cancer is an illness associated with aging, as well as high prevalence of multi-morbidity [55].

Evidence suggests that the number and severity of comorbidities at the time of a cancer diagnosis is strongly related to death due to non-cancer causes and cancer-specific mortality [56–59]. Health disparity populations are more likely to have multiple morbidities that require coordination of care for the management of several health conditions. Therefore, suboptimal survival outcomes among cancer survivors from health disparity populations are attributed, in part, to higher incidences of comorbidity that significantly contributes to increased disability and mortality [60–62].

Furthermore, health disparity populations often seek care in resource poor primary care settings [63]. In a study of racially diverse cancer survivors between the ages of 40 and 84 years, African-American women had the highest rates of chronic disease comorbidity (76%) followed by African-American men (70.6%) [64]. This finding and others suggest that the compound impact of cancer and comorbidity among African-Americans may be a significant contributor to poorer survival outcomes [61, 65, 66]. While survival is a key outcome, data are scarce on the impact of multi-morbidity on long-term health of cancer survivors and health disparate cancer survivorship populations. Additional research is needed to explore the impact of multi-morbidity on factors such as quality of life, self-management, and healthcare access and utilization.

5.4 Opportunities to Reduce Health Disparities

Cancer survivorship, similar to other transition points across the cancer care continuum, can be burdensome and difficult to navigate for low-income,

uninsured or underinsured, racial/ethnic minority, and other medically underserved cancer survivors who face additional barriers to accessing care and maintaining care continuity [67, 68]. The Institute of Medicine's 2013 report titled "Delivering High-Quality Cancer Care" declared a crisis in cancer care delivery [69]. This report and other studies document that low-income and racial/ethnic minority cancer patients, particularly those with Medicaid coverage or those without insurance, are more likely to experience delays in care, less likely to undergo cancer treatment, and have worse survival compared to privately insured or Medicare-insured groups. Many cancer patients who rely on charity/indigent care or emergency public insurance coverage during the diagnosis and treatment phases of the cancer care continuum face additional financial, geographic, and social barriers to receiving long-term follow-up care after active cancer treatment. Even among cancer patients with insurance, previously imposed lifetime insurance coverage limits and increasing out-of-pocket costs can cause severe hardships or affect access to necessary follow-up care [47, 54, 70].

5.5 The Affordable Care Act

The implementation of the Affordable Care Act (ACA) in 2010 resulted in 20 million Americans gaining health insurance [71]. Prior to the ACA, an estimated 14.7% of survivors were uninsured, and 18% of this population reported having a financial hardship. It was estimated that 30% of uninsured cancer survivors would become eligible for health insurance upon ACA implementation [72]. Approximately 2.1 million Medicaid enrollees are cancer patients or cancer survivors across the United States [73]. ACA coverage requirements specified the following provisions for patients with cancer, including coverage of cancer screening, preventive care, and clinical trials, as well as protections against lifetime spending caps, annual limits, and differential rates because of preexisting conditions [74]. These provisions are important for the prevention of complex sequelae, as uninsured cancer survivors are less likely to receive preventive care, including cancer screenings [75], and are more likely to be diagnosed with later stage second cancers which have poorer prognosis [76]. While these important gains have provided proximal access to treatment and short-term follow-up as well as reduced financial hardship, it is unclear how proposed changes to the ACA will affect the receipt of cancer survivorship care across population subgroups in the years to come [77].

5.6 Care Transitions

In the US healthcare system, care transition points are replete with opportunities for system failures, and the transition from acute cancer care to post-acute care routinely lacks proactive coordination [78]. The Centers for Medicare and Medicaid Services (CMS) defines a transition of care as the movement of a patient from one setting of care to another. Settings of care may include hospitals, ambulatory primary care practices, ambulatory specialty care practices, long-term care facilities, home health, and rehabilitation facilities [79].

Following post-acute care, primary care providers are increasingly poised to be more involved in the follow-up care of survivors [80–85]. Yet, during the transition from acute cancer care to long-term cancer survivorship follow-up, patients are not confident with their PCP level of cancer follow-up expertise [86, 87], physician training and education on survivorship issues is limited [80, 88, 89], and barriers to patient and provider communications exist [86]. While several care transitions initiatives have been implemented or piloted by the Agency for Healthcare Research and Quality (AHRQ) or CMS to improve transitions between acute hospitalizations and long-term care or back to primary care [90, 91], few strategies have been developed to focus on improving the transition from active cancer treatment to long-term survivorship care.

5.7 Policy and Interventions to Reduce Health Disparities

Three broad strategies have been used to overcome the issues of fragmentation and coordination among the diverse cancer survivor populations: (1) the piloting of cancer survivorship models of care, (2) the development of survivorship care plans, and (3) the use of patient navigation services. The advent of cancer survivorship care models are often extension models already describing oncology settings [64, 92]. Most of these models implemented are extensions of oncologic care but vary widely in approach and scope of care based on the context where they are operationalized [64, 93]. This lack of standardization has been identified as a key care quality issue in survivorship care and remains a critical obstacle to developing strategies that are responsive to health disparity populations [2]. Further, studies of these survivorship models that have been piloted thus far have not consistently reported the proportion of non-White survivors who have access to these innovative new care models being studied [64, 94]. Unfortunately, no reliable information about how accessible cancer survivorship programs are to minority and underserved populations of cancer survivors in the United States is available [94].

The second strategy to overcome fragmentation during post-acute cancer care is separate, but related to piloted models of survivorship care, and is often a key focus of these models—the provision of a survivorship care plan (SCP). Survivorship care plans have been proposed as a communication tool intended to bridge the identified communication gap between patients, acute cancer care providers, and primary care physicians [95] and in some cases have been culturally tailored to address differences specific to subpopulations. A SCP can be a hard copy or electronic document that includes a personalized treatment summary, information on possible late- and long-term effects, signs of recurrence, guidelines for follow-up care cancer screening and surveillance tests, recommendations for healthy living, and identification of supportive care resources [96–98]. The American College of Surgeons has made the provision of survivorship care plans a requirement for cancer center accreditation, which was endorsed by the American Society of Clinical Oncology as a step toward the delivery of higher-quality cancer care [99]. While primary care physicians are more likely to report engaging in survivorship care planning upon receipt of a care plan [100], evidence suggests care plans were not significantly efficacious in improving clinical and patient-reported outcomes [101, 102]. To date, no efficacy trials have investigated the feasibility of dissemination and potential impact of using survivorship care plans on clinical and patient-related outcomes in health disparity populations.

There are several potential reasons why SCPs may not fully address health disparities in cancer survivorship. Parry and colleagues [103] describe a "shortcoming of existing survivorship care planning is that it has not adequately addressed the diverse sociocultural backgrounds that survivors bring with them into the care context." Because the emphasis is on transitioning survivors from acute cancer care to primary care, the current care planning process does not attend to whether survivors have a usual source of care. Recent studies have shown in non-Medicaid expansion states, cancer survivors were more likely to lack a usual source of care and report being unable to afford medical care [104].

Additionally, several studies have explored the acceptability of SCPs in minority populations and key findings indicate traditional SCPs: (1) are too technical, (2) use a "one-size-fits-all" communication strategy, (3) contain excessive medical jargon, (4) neglect psycho-social and self-care needs, and (5) do not provide sufficient information about late- and long-term effects of treatment [105–107, 86, 108]. These research studies have also noted that standard SCP templates do not sufficiently address well-documented factors such as personal beliefs and traditions; spirituality, culturally, and linguistically appropriate information; and medical mistrust that may impact their implementation [105, 109, 107, 110, 111, 108]. A 2013 study using

consensus meetings with survivors and advocates to identify culturally responsive SCP content and domains [105] found that SCPs lack patient input and adequate information on health histories, comorbidities, and health promotion. Recommendations to improve SCPs included documentation of all comorbidities and medications regardless of relationship to cancer, referrals for cancer-related providers, and culturally informed health advisories [105].

Studies that have sought to explore cultural adaptations of SCP content and delivery strategies provide many suggestions for culturally tailoring these tools based on the preferences and needs of specific populations. For example, Chinese-American breast cancer survivors preferred to receive their initial treatment summary face-to-face encounter with a provider, followed by a lay language written summary in English and Chinese [110]. A study of low-income survivor populations' concerns reported that a SCP should not replace direct communication with providers; however, there was a need to develop low-literacy written information in multiple languages [112]. Findings from research among African-American breast cancer survivors suggest that survivors received variable amounts of information about their cancer treatment and were unhappy with the cultural and race-specific information received [107].

The third strategy used to overcome health disparities are patient navigation services. Patient navigation services—a barrier-focused interventional approach to address and overcome fragmentation of care issues—have emerged as a strategy to address and overcome health delivery-related disparities across the cancer continuum for racial/ethnic minorities [113–116] and low-income [117, 118] and other urban underserved populations. These patient navigation strategies have utilized both medically trained staff and lay health workers and *promotoras.* According to a review of the state of the science regarding patient navigation, these efforts are largely focused on cancer screening, diagnosis, treatment, and clinical trial enrollment [119]. Although a qualitative study of African-American breast cancer survivors describes the need for continued navigation during post-acute care [120], to date, no efficacy studies have evaluated the impact of patient navigation services on survivorship outcomes [119]. Currently, there is no other research to inform this area regarding disparity groups; therefore, subsequent research to expand the evidence base and articulate best practices for patient navigation during the cancer survivorship phases of care are warranted.

5.8 Future Directions

Evidence regarding the incidence and mortality for key racial and ethnic minority subpopulations in the United States is readily available and can assist in the development of cancer prevention and control strategies to address health-related outcomes. However, additional research is needed to further elucidate drivers of health disparity cancer survivorship outcomes at the individual, social, and health system process levels that contribute to physical and mental health quality of life during survivorship, from the period of post-acute cancer care to the end of life. The current race and ethnicity data collected nationally in datasets such as NCI's Surveillance Epidemiology, and End Results (SEER) are systematic but not comprehensive; therefore, the current practice of lumping smaller subpopulations together into heterogeneous groups to achieve larger samples makes it difficult to discern whether trends noted at the population level translate into actionable data for use at the individual, social, and health system process levels. While race and ethnicity data are insufficient, there is a lack of data regarding sexual minorities health research as documented in the recent IOM report [24], and current national resources such as the SEER database do not collect data on sexual orientation or gender identity. Therefore, to address health disparities in cancer survivorship, we need more data about individual groups for tailoring and use in design and implementation of specific cancer prevention and control program and policy-making efforts.

There is also need for interventions to address the disproportionate burden of multi-morbidity in particular among the underserved. The need to further tease apart the cumulative impact and relationships between obesity, comorbidities, race, and ethnicity on cancer survival and survivorship outcomes has been articulated elsewhere [14]. Additionally, the potential impact of financial toxicity on poorer health outcomes among health disparity populations is an area in need of additional attention. Much of the focus thus far has been on the impact on insured populations [50], whereas more studies of the uninsured and underinsured are needed. Further, existing SCPs do not adequately address the needs of diverse minority populations [105, 107, 110, 109]. The potential of survivorship care plans that incorporate the culture, values, and beliefs of minority cancer survivors to reduce barriers in communication and improve coordination of care is an area in needs further research [107, 105, 121, 122].

The issues described above point to a growing appreciation for the development of multilevel interventions [123]. Interventions that move beyond framing health outcomes as the result of individual choice and instead acknowledge that health is the result of individuals and groups navigating complex social and political environments are needed [124]. Inequalities based on race, income, and sexual identity should be conceptualized from an intersectional approach that understands that vulnerabilities for health disparities may be multiplied and compounded [125]. As is the case for many health issues, disparities in cancer survivorship manifest at multiple levels, such as home/family, community, region, state, and health service delivery. Therefore, issues such as poverty, race, and how these manifest within communities influence crucial behaviors. Policy can shape health system responses that impact the cancer survivorship phase of care. It is important that cancer survivorship disparity research evolve to address this multilevel, social ecological context.

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Aging

6

Leah L. Zullig, Christina D. Williams, and Harvey J. Cohen

6.1 Overview of Aging and Cancer Burden

With the rising numbers of baby boomers moving into the older age groups, the well-known relationship between aging and cancer, the earlier diagnosis, and the increasing survival of this group following primary cancer treatment, there is no question that the attention paid to this group in terms of research and clinical care is on the rise. This chapter provides a review of common concerns and the management of this relatively forgotten group in the areas of cancer survivorship research and practice.

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6.1.1 Physiologic Versus Chronologic Aging

Aging, in the simplest term, refers to the process of becoming older. Physical aging can be characterized by four major "losses": (1) loss of speed, (2) loss of flexibility, (3) loss of acuity, and (4) loss of stamina [1]. In scientific literature, there is variability in what is meant by "older" and "elderly" populations. Many studies among patients with cancer, particularly those using SEER-Medicare data, use 65 years of age as a threshold to define elderly [2]; however, some studies use minimum ages of 60, 70, or 75 years when referencing older cancer patients. Differing definitions of "older" can make comparisons across published works challenging. Additionally, there is heterogeneity in overall health and wellness among people by age, particularly among older cancer survivors. As an example, consider two 80-year-old men, both who recently completed treatment for early stage non-small cell lung cancer. The first man walks 3 miles daily, regularly takes gentle water aerobic classes on the weekends with his wife, and has well-controlled hypertension as his only comorbid condition. The second man has been sedentary for most of his adult life and does not currently exercise. He is socially isolated and has comorbid diabetes and congestive heart failure.

While there is an inverse association between chronological age and physiological age, the

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differences in health status among older individuals with a history of cancer vary due to several factors, including genetic, environmental, and lifestyle [3]. The aforementioned case examples illustrate age alone does not tell the full story. This heterogeneity among older cancer survivors is often underestimated and potentially contributes to age-based disparities in cancer care, such as undertreatment and underrepresentation in clinical trials [4, 5]. Therefore, while age is an important factor of cancer survivorship care, it is not a sufficient proxy for health status upon which to base decisions of cancer management and support.

6.2 Increasing Prevalence and Needs of Older Cancer Survivors

There are an estimated 15.5 million cancer survivors living in the USA, and 62% of survivors are 65 years or older [6]. As efforts to improve the diagnosis and management of cancer continue and as our population is aging, the proportion of older cancer survivors is expected to substantially increase [6]. Over the next two decades, the number of cancer survivors overall is estimated to nearly double to 26.1 million; approximately 73% of cancer survivors in 2040 are anticipated to be 65 years and older, and among these survivors, 31% will be 75–84 years of age, and 18% will be 85 years and older [6].

Due to cancer and associated treatment, cancer survivors face many physical and mental health effects. As the number of older cancer survivors (i.e., those aged 65 years and older) increases, we must understand and address the differing health needs of this unique population. Many older individuals have multiple chronic conditions, functional and cognitive decline, and physical limitations that may be exacerbated by cancer treatments, as well as impair prognosis and quality of life [7, 8]. While about half of survivors aged 70–74 years do not experience multiple chronic conditions prior to their cancer diagnosis, there is a considerable increase in the prevalence and severity of multiple chronic conditions with increasing age [6]. Consequently, these patients can experience fragmented care and receipt of suboptimal management of these multiple chronic conditions.

Older cancer survivors are unique for several reasons. The physiologic changes of aging, such as that leading to decreased organ function (e.g., decreased wound healing, renal, cardiac, and immune function), may impact treatment decisions and outcomes. Older patients may present with disorders and treatment complications in a different manner and exhibit greater psychological resilience than younger survivors [9]. Emerging evidence suggests that older cancer survivors with good baseline physical function, high self-efficacy, and strong social support may also be physically resilient [10]. Adverse outcomes due to coexisting cancer and chronic illnesses may cause survivors to need more support services and be concerned about losing their independence [11]. Therefore, older individuals represent a vulnerable population of cancer survivors. They present the need for additional assessment of multiple chronic conditions, socioeconomic conditions, functional dependence and frailty, and cognitive conditions [12]. In this chapter, we discuss characteristics of older survivors, late effects of treatment, unique needs, and the implications for survivorship care for older patients.

6.3 Clinical Characteristics of Older Cancer Survivors

6.3.1 Comorbidity

A particularly salient issue among older cancer survivors is the increased likelihood of multiple competing medical conditions and difficulty isolating cancer-related effects due to comorbid conditions. Data suggest that at least 80% of older adults in the USA have at least one comorbid condition and half of the older adult population has two or more comorbidities [13]. In a study by Bluethmann et al. [6], the authors noted that the medical history of severe comorbidity (defined as the presence of conditions that usually

require modifications to cancer treatment, such as chronic renal failure, liver dysfunction, COPD, dementia, AIDS, CHF), among older cancer survivors, ranged from 26% in the 66–69 age group to 47% in the 85+ age group, compared to 16% to 42% among older non-cancer survivors [6]. While comorbidities are highly pervasive among older cancer survivors, the prevalence of most medical conditions at diagnosis and incidence after diagnosis were similar among older (≥60) cancer survivors compared to older non-cancer survivors [14]. However, in the same cohort of approximately 3,800 cancer patients and 12,000 non-cancer patients, COPD and venous thrombosis were more common among older people with a history of cancer than those without. There is a possibility that this is a survivor effect in that those who were older and had more comorbid conditions have died, and are thus not included in the studies.

Likewise, among older adults, the most commonly occurring comorbidities are similar for among people with and without a history of cancer [6, 15]. Despite the high prevalence of comorbidity among the elderly, it remains unclear whether comorbidities affect older cancer survivors differently than those without cancer. For example, the extensive and severe comorbidities in older adults may affect the type and response to cancer treatment and physical resilience to side effects and can even be exacerbated by cancer-related toxicities [16, 17]. Also, cancer diagnosis and treatment in older adults can accelerate development of subsequent conditions. Common sequelae of cancer treatment include second malignancies, cardiovascular disease, and development of diabetes and osteoporosis [14]. Other physical effects and symptoms of cancer include pain, fatigue, sleep disturbance, and cognitive dysfunction [3]. Some of the most clinically important effects in older cancer survivors include fatigue and pain [18], peripheral neuropathy [19], bone health [20, 21], and cognitive decline [22]. Pain and fatigue, in particular, are known to be associated with functional decline in older survivors [23], and the severity of symptoms is strongly correlated with multiple comorbidity and posttreatment functional decline in older cancer patients [24]. These potential late effects of cancer and its treatment can often be mistaken as normal aging rather than as cancer-related treatment effects. This emphasizes the need for ongoing assessment of long-term and late effects of cancer symptoms considering the presence, severity, and burden of cancer-related symptoms in older cancer survivors (Table 6.1). Therefore, while the prevalence of comorbidities in older cancer survivors is greater than younger cancer survivors, yet similar to older non-cancer patients, the severity, implications, and short-term consequences of these conditions are unique to older cancer survivors and often require special consideration.

6.3.2 Polypharmacy

With age comes an increasing prevalence of multiple chronic conditions and an increasing reliance on multiple medications, or polypharmacy, to manage chronic conditions. Polypharmacy is broadly defined as the prescription and utilization of multiple medications to treat coexisting illnesses and symptoms [25] and/or the inappropriate use, underuse, or overuse of medications [26]. Older cancer patients are not only on multiple medications to treat cancer and manage symptoms and side effects but also to manage other pre-existing and newly developed chronic conditions. A cancer diagnosis will often necessitate the use of medications to treat the cancer, reduce the likelihood of recurrence or new malignancies, and counteract potential complications or side effects of medications used for cancer treatment. Polypharmacy is common in older adults in general and has been found to be more common in older cancer survivors compared to both younger cancer survivors and to older individuals without cancer [27]. Other studies that have evaluated polypharmacy in older cancer patients have reported 35–80% of older patients (age ≥ 65 years) were taking at least five drugs at the time of the cancer diagnosis [27–29]. Approximately 40% were taking potentially inappropriate drugs [28], and about 30% had a potential drug-drug interactions [30]. A recent

Table 6.1 Potential late effects from cancer treatment

Organ system	Potential late effects
Cardiovascular	Coronary artery disease Pericardial effusion Pericarditis Cardiomyopathy Atherosclerotic cardiovascular disease Arrhythmias Valve dysfunction
Pulmonary	Interstitial pneumonitis Pulmonary fibrosis Restrictive lung disease Obstructive lung disease Decreased lung volume
Renal and genitourinary	Glomerular toxicity Tubular dysfunction Erectile dysfunction Dyspareunia Decreased creatinine clearance Hypertension
Sensory	Hearing loss Tinnitus Decreased vision Cataracts Retinopathy
Endocrine	Osteoporosis Obesity Metabolic syndrome Hypothyroidism Premature menopause
Hematologic	Cytopenia Myelodysplasia
Neurologic	Leukoencephalopathy Stroke Cerebellar dysfunction Cognitive dysfunction
Dental and oral	Poor enamel and root formation Dry mouth Tooth decay
General	Fatigue Financial distress

Material in Table 1 was adapted from Aziz et al. 2017 and Henderson et al. 2014 [34, 47]

study among breast cancer survivors who were prescribed with oral medications for the management of chronic conditions found that adherence to those medications decreased sharply after breast cancer treatment (91.4% before treatment to 77.9% after treatment, $p < 0.001$) [31].

Additional negative implications of polypharmacy, such as decreased medication adherence and increased cost, are likely to be worse in older cancer patients relative to their younger counterparts. Optimal management of polypharmacy in older cancer survivors should, at a minimum, include periodic medication reconciliation (pharmacy review) and management by an interdisciplinary team that includes a clinical pharmacist [25]. One tool to evaluate polypharmacy in older adults is the ARMOR (Assess, Review, Minimize, Optimize, Reassess) tool [32]. The ARMOR consolidates many clinical recommendations about polypharmacy into a functional, stepwise tool that guides clinician through an action-oriented polypharmacy assessment.

6.3.3 Functional Status and Changes

As a result of multiple morbidity, physiological decline, and the effects of cancer treatment, older cancer survivors have greater risk of physical limitations and disability. In older cancer survivors, the purpose of treatment and follow-up care is not only to prolong survival but also to maintain function. For many patients, maintaining functional status and independence may be equally as important as prolonging survival (see Sect. 2.3 describing patient preferences and decision-making). Functional status is strongly associated with a patient's ability to tolerate treatment and predicts mortality [33]. However, long-term cancer survivors are subject to worse functional status than the non-cancer elderly population [34]. Functional decline can persist throughout survivorship but is most significant in the first few years after treatment [35]. Studies of newly diagnosed cancer patients indicate worse cancer-related physical function among older patients than younger patients [35]. Since one of the best predictors of subsequent physical function is baseline physical function, it may be worth considering older adults' baseline physical function, function during treatment, and following treatment. Most studies have not captured functional status prior to the cancer diagnosis, making it difficult to tease out the effect of cancer.

Functional status, also referred to as performance status, is probably the single most important determinant of optimal therapy in oncology

and predicts future functional status. Functional or performance status can be assessed using three approaches: (1) observational, retrospective data-driven measures (e.g., Eastern Cooperative Oncology Group Performance Status or ECOG PS); (2) observed, objective measures (e.g., functional gait assessment); or (3) technology-based measurements (e.g., physical activity monitors). While these measures assess slightly different aspects of physical function, it is important to note that performance status assessments are associated with response to chemotherapy, survival, and quality of life [36]. Two of the most common tools for retrospective data-driven assessment of performance status are the Eastern Cooperative Oncology Group performance status (ECOG PS) and the Karnofsky Performance Status (KPS) scales. However, validation of these tools is scarce and limited in the younger cancer population (i.e., mean age of 50) and therefore may not accurately capture the functional variability in older persons [37].

Alternative measures of performance status such as the comprehensive geriatric assessment (CGA), which evaluates multiple domains of older patients including functional status, may be more appropriate [38]. The CGA has been shown to provide more information on performance status in older cancer patients compared to the ECOG PS alone [39] and impact treatment decisions [40] (see Sect. 4.3). Two predictive models have been developed to address limitations and supplement performance status measures, particularly for evaluating older patients' eligibility for chemotherapy. The Cancer and Aging Research Group (CARG) score categorizes patients ≥65 into three categories (high, medium, low) of chemotherapy toxicity [41], and the chemotherapy assessment scale for high-age patients (CRASH) score predicts for hematologic and non-hematologic chemotherapy toxicities and categorizes patients into four risk groups (low, medium low, medium high, high) [42]. Observed objective measures of physical function include the functional gait assessment, timed "up and go," and dynamic gait index, among others [43, 44]. While in their infancy in clinical practice, wearable physical activity monitors also hold promise for informing providers about the actual physical activity of their older cancer patients [45]. When assessing performance status in older cancer patients, it is critical to apply the most appropriate assessment tool or combination of tools [46].

6.3.4 Frailty

Physiologic reserves decline with age; thus older individuals may be more vulnerable to disability and morbidity. This physiologic decline can manifest as reduced energy metabolism and loss of neuromuscular function, for example, and can be amplified by acute injury or pre-existing illness and lead to permanent organ damage [47]. Frailty was initially described as a syndrome characterized by decreased homeostatic reserve and resistance to stressors [48] and is a result of the cumulative decline across many organ systems and therefore increases risk of adverse outcomes. There are two common approaches to measuring frailty: (1) the deficit-accumulation frailty index [49] and (2) the frailty phenotype index [48]. These approaches are applicable to all older patients and, thus, are applicable for both cancer treatment and survivorship care.

The deficit-accumulation frailty index captures the influence of a multitude of age-related health deficits that include symptoms, signs, diseases, disabilities, or other test abnormalities [50]. It is calculated by dividing the sum of all health deficits a person has by the total number of possible health deficits considered [49]. 1 and 0 indicate presence or absence of a deficit, respectively; therefore, the resulting index score is between 0 and 1 where 1 represents complete frailty and 0 represents complete health. Although there is no standard set of potential deficits that must be considered in a given frailty index assessment, each deficit must (1) increase with age, (2) be health-related, (3) be prevalent in at least 1% of the study population, (4) be absent in 80% of the study population less than 80, and (5) be non-missing in more than 5% of the study population [51]. A recent study using a modified frailty index found that a high frailty index (>0.27) was associated with increased incidence of

postoperative complications and 30-day mortality among older (ages 60–90) gastrointestinal cancer surgery patients [52]. A comprehensive geriatric assessment (CGA) is often used to assess frailty in older cancer patients [53]. Cohen et al. used the CGA to create a deficit-accumulation frailty index among older patients scheduled to begin a new chemotherapy regimen [54]. Using this approach, the authors classified 50% of patients as non-frail, 39% pre-frail, and 11% frail, and pre-frail/frail patients had increased risk of grade ≥ 3 toxicity, discontinuing chemotherapy, and being hospitalized [54].

The frailty phenotype index, another common tool for defining frailty, can be conceptualized by the presence of at least three of the following characteristics: unintentional weight loss, exhaustion, low energy expenditure, slow gait speed, or weak grip strength [48, 55]. Using this frailty phenotype index, the prevalence of frailty in a cohort of Medicare patients was significantly greater among those with cancer (79.6%) compared to those without a history of cancer (73.4%) [56]. There are a number of validated tools that can be used to measure frailty and are considered to be on a spectrum between the deficit-accumulation frailty index and the frailty phenotype index [57]. The comprehensive geriatric assessment is a recommended tool for diagnosing frailty among older patients [58] (see Sect. 4.3), and the NCCN guidelines recommend using a geriatric assessment in older cancer patients to define their physical, psychosocial, and functional well-being, including frailty [46].

A systematic review related to the prevalence and outcomes of frailty in older cancer patients has been recently conducted [55]. The studies included in the review defined frailty using the deficit-accumulation frailty index, frailty phenotype index, or CGA [55]. This systematic review found that the median prevalence of frailty was 42% and that frailty was associated with increased risk of all-cause mortality, postoperative mortality, and treatment complications. Even those classified as pre-frail (i.e., 1–2 of the 5 frailty characteristics) had increased risk of premature mortality [55, 59]. The prevalence of frailty may vary depending on the instrument used; however, despite the method used to diagnose frailty, it is correlated with significant morbidity and mortality. Detecting frailty in older patients with cancer can aid in risk stratification and thereby ensure that elderly frail patients are not exposed to treatments for which they are unable to tolerate and that elderly fit patients are considered for guideline- or consensus-based treatments.

6.3.5 Cognitive Changes

Changes in multiple organ systems increase with age, and changes in the brain affect cognitive function. Aging, in general, is characterized by increased damage to cellular processes, diminished reserve, susceptibility to disease, and resistance to stressors, which collectively contribute to cognitive impairment [60]. Multiple morbidities in older patients can also directly or indirectly affect cognition. For the older cancer survivor, cognitive impairment has implications along the survivorship continuum including understanding prognosis and treatment options, decision-making, treatment adherence, symptom management, recommended follow-up care, and additional caregiver support [3]. Not only can pre-existing cognitive impairment affect cancer care, but studies also suggest that systemic therapy in older cancer patients can contribute to impairment of one or more cognitive domains, although the biological mechanisms are currently unclear [22].

Investigations of cognitive decline following systemic cancer therapy have shown conflicting results, and most work in this area has been between breast and prostate cancer survivors. For example, Jean-Pierre and colleagues sought to determine the prevalence of self-reported memory problems in a USA based nationally representative cohort of patients with and without a history of cancer [61]. Among this sample, patients with a history of cancer reported memory problems more often than those without a history of cancer (14% vs. 8%). Another large cohort study of older (aged 65 years and older) survivors of nonmetastatic breast cancer found that approximately 42% of survivors maintained

high self-reported cognitive function and a minority (approximately 8%) reported accelerated cognitive decline [62].

While some older cancer survivors may experience minimal cognitive decline associated with the aging process, others may experience more significant cognitive changes including dementia. At present, there is no consensus, and the clinician should use treatment measures he or she is most comfortable with depending on data available. For example, of two studies evaluating the correlation between dementia and chemotherapy among older breast cancer survivors in the SEER-Medicare population, one found no association [63], while the other observed higher risk of dementia in patients who received chemotherapy compared to those who did not [64]. Similarly, among older (≥70) men with prostate cancer, the 5-year cumulative probability of being diagnosed with dementia was 13.7% for those receiving androgen deprivation therapy (ADT) compared to 6.6% for those with no ADT (differences were much smaller among younger patients, i.e., 2.3% vs. 1.0%) [65].

Manifestations of cognitive impairment are also known to be a predictor of mortality among older cancer patients. In a longitudinal study of older (≥65 years) cancer patients in Belgium who had breast, colorectal, or prostate cancer surgery, 46% had some level of cognitive impairment based on the Montreal Cognitive Assessment, and those with cognitive impairment were six times more likely to die within 2 years than patients without cognitive impairment [66]. In this study, most deaths among all patients were attributed to cancer progression.

While mechanisms underlying the relationship between cognitive changes and cancer treatment and outcomes are still being explored, evidence to date at least warrants screening for cognitive impairments prior to initiating cancer treatment and also throughout survivorship. Few pharmacological agents have been tested for efficacy against cognitive decline, and nonpharmacological interventions such as psychosocial support and cognitive behavioral therapy have been considered in the management of cognitive impairments, particularly chemotherapy-induced cognitive decline [67, 68]. However, there remains a need for guidelines for screening and management of cancer treatment-related cognitive dysfunction.

6.3.6 Psychosocial Considerations

Many social factors may differ in the care of older cancer survivors as compared to their younger counterparts. These factors include the lack of a spouse or other family members in the home, fixed incomes, and the living arrangement (e.g., independent vs. assisted/facility living) [69]. Among older adults with cancer, social isolation and loneliness are established predictors of mortality [70], as well as increased risk of anxiety and depression [71]. Depression can contribute to functional decline but also be an indicator of additional needs for social support and caregiving [72]. Despite the potential role of depression in managing these cases, depression often goes undiagnosed and undertreated due to atypical presentation in older patients (e.g., somatic symptoms such as sleep disturbance, body aches, and malaise are more common in older patients compared to younger adults) [73, 74].

Older cancer survivors are more likely to have older companions and caregivers who may have their own health problems, so understanding the type and extent of support (e.g., travel, financial, social, dietary, etc.) available may impact treatment decisions. The outcome of treatment decisions should be weighed carefully. Informal caregivers for older cancer survivors, often friends and family members, frequently report high levels of distress and low levels of social support and coping abilities [75]. The potential negative impact on caregivers' well-being may cause a negative cycle that subsequently impacts the survivors' well-being. Thus, caregiver burden is an important psychosocial consideration for both members of the survivor-caregiver dyad.

While there are no clear guidelines for caregivers of cancer patients, some professional organization such as the American Cancer Society and National Cancer Institute provides guidance and resources for cancer caregivers [76, 77].

Also, those caring for older (≥65) patients have been classified as "vulnerable" caregivers, while caregivers of younger patients are considered "non-vulnerable," because there are increased physical, emotional, and financial demands and strains associated with caring for older patients with cancer [78]. Despite the potential psychosocial distress of caregiver, older survivors may exhibit greater psychological resiliency due to well-established, long-term interpersonal relationships that provide support [9].

6.4 Financial Burden

Managing the physical toxicities of cancer treatment has been the focus of researchers and clinicians for decades; however, the importance of managing the financial toxicities resulting from cancer – both during and after treatment – on older adults has only recently been recognized. Financial toxicity encompasses both objective financial burden and subjective financial distress [79]. Out-of-pocket expenses related to cancer treatment are akin to physical toxicity because, just as physical toxicities negatively impact patients' quality of life and the ability to deliver the best quality cancer care, so too do financial toxicities [79].

The financial toxicities of cancer treatment are problematic for cancer survivors of all ages but may be particularly devastating for older cancer survivors who may be forced to spend their savings at a time when they would traditionally be focused on retirement. Another study found that, compared to men without a history of cancer, male cancer survivors are less likely to be employed, more likely to be retired, and were less optimistic about finding a job [80]. This study was conducted among men age 55 years or older, potentially a decade before becoming eligible for Medicare. For older cancer survivors who have not yet aged into Medicare, lapses in employment could cause insurance gaps and necessitate spending down of personal and retirement savings. This is particularly problematic for older cancer survivors who are in or approaching retirement.

In the era of cost sharing and coinsurance, patients with cancer increasingly shoulder the financial burden of their care. One study showed that cancer patients pay an average of $700 per month for their cancer care, despite having insurance (mean age = 64 years) [81]. Patients are sensitive to even small financial changes in co-payments. Among patients with chronic myeloid leukemia, one study showed a median co-payment of $30 [82]. Patients with higher co-payments were 42% more likely to be nonadherent with their oral anticancer treatment [82]. Older cancer survivors living in rural areas may be especially at risk for financial burden. Older rural cancer survivors are approximately 66% more likely to forgo medical care and were 54% more likely to avoid dental care than those in urban areas, due to cost [83]. It is important to note that even though many older cancer survivors may qualify for health insurance coverage through Medicare, there may still be substantial co-payments for cancer treatment and follow-up services, particularly for newer biologic and immunotherapy oral medications.

There are many programs designed to provide financial support for people struggling to afford their cancer treatment (i.e., pharmaceutical patient assistance programs, financial counseling services). However, the financial burden of cancer care may still be experienced by those who seek financial assistance. Among patients enrolled in a national co-payment assistance program, 45% reported cost-related treatment nonadherence (e.g., not taking prescription medications as prescribed) [84]. While older age was associated with less cost-related nonadherence, cost-related nonadherence did persist even among older cancer survivors. On average, cost-related nonadherent patients were 70 years old, and this nonadherence took several forms. Patients reported taking medications prescribed for someone else (4%), taking less of a medication that was prescribed (22%), only partially filling a prescription (25%), not filling a prescription (27%) – all because of cost [84].

Even cancer survivors with health insurance coverage report altering their care or lifestyle to afford their cancer care. Cost-related

nonadherence has also been documented among elderly patients both with and without a history of cancer who were insured through Medicare [85]. Among elderly cancer survivors with Medicare, approximately 10% reported cost-related nonadherence. Compared to adherent patients, these older cancer survivors who reported cost-related nonadherence had lower incomes and were more likely to be of African-American race [85]. Again, this is often at a time when patients are in or approaching retirement and will increasingly rely on accrued savings.

Cancer patients and survivors may not seek financial assistance because they are not aware of the potential severity of their financial burden until after treatment choices have been made. A study among older breast cancer survivors revealed that there is a need for prompt information about anticipated treatment costs and insurance coverage and for physicians to become aware of cancer costs and financial issues faced by patients and consider costs in their treatment plans [86]. Cancer patients may have difficulty articulating their financial needs [87]. Very few patients report discussing treatment costs with their providers [88].

6.5 Patient Preferences and Decision-Making

Older patients with cancer may be presented with different treatment options than their younger counterparts, usually due to perceived contraindications including multiple chronic conditions or reduced functional status [89]. However, older patients are also at risk of undertreatment because of limited understanding of their diagnosis, prognosis, and treatment options. Clinical trials provide the evidence base for treatment decisions, but older adults are underrepresented in most trials [90]; thus, providers have relatively little evidence on which to base their clinical recommendations. Lack of data from clinical trials that enrolled older adults may mean that there is an insufficient understanding of potential physical toxicities to cancer treatment for which older cancer survivors may be more susceptible. For example, older chemotherapy medications had well-documented short-term side effects (e.g., nausea and vomiting), but the potential long-term side effects of newer biologic and immune therapies are not as well known (e.g., development of hypertension, peripheral neuropathy, and other chronic conditions). Older adults should be presented with opportunities to engage in clinical trials, both to support an individual's access to cutting-edge cancer treatments and to inform the field's understanding of best treatment practices for older adults. Failure to engage in such discussions with older adults may result in their receiving treatment that is inconsistent with their preferences.

Providers' treatment recommendations should be based on older survivors' clinical conditions, functional status, life expectancy, and preferences [91]. Older cancer survivors may have unique values that should be factored into treatment decision-making – maintaining independence, the ability to perform daily activities, and control of their health [92]. Younger (e.g., ≤60–65) patients may prefer treatment that they believe will increase life expectancy, while older (>65) patients prefer that which will increase quality of life and preserve independence [93–95]. In older patients, the balance between quantity of life and quality of life is a challenge in the decision-making process. In decision-making, few elderly patients want information on expected survival. In a study of older (70–89 years) patients with metastatic colorectal cancer, about one-third wanted information on prognosis [91].

6.6 Late Effects of Treatment

Older cancer survivors experience the negative synergistic effects of biologic and physiologic changes due to chronological aging and increased morbidity common to older persons in general but also the late effects of both the cancer and its treatment (Table 6.1). These changes are typically manifested by reduced capacity in organ and homeostatic reserves and can persist throughout survivorship. Late effects of cancer treatment specifically refer to undiagnosed toxicities at the

completion of initial therapy that rather manifested months to years later. These toxicities can be acute, such as radiation pneumonitis, or chronic, such as congestive heart failure. In general, chemotherapy toxicities are acute, whereas radiation therapy toxicities do not become apparent for some time, as is the case for combinations of chemo- and radiation therapy. Late effects can be further categorized as system-specific, second cancers, functional changes, cosmetic changes, and associated comorbidities. They are often specific to the type of therapeutic exposure. Organs and tissues most susceptible to the effects of chemotherapy drugs are those with high proliferation rates (e.g., skin, liver, gastrointestinal mucosa), while less susceptible organs and tissues are those that replicate slowly or not at all (e.g., connective tissue, muscle cells) [34]. However, certain chemotherapy drugs such as methotrexate can cause neural damage and bone injury as well.

All types of cancer treatment can affect all organ systems to some extent; however, chemotherapy has the greatest systemic effect [47]. Most chemotherapy drugs either inhibit DNA synthesis or promote DNA damage, which can contribute to the development of a second cancer, accelerated aging, or both [96]. For example, patients given the platinum-based chemotherapy drug cisplatin can experience long-term side effects such as irreversible hearing loss and permanent renal and neuronal damage [97] that resemble accelerated aging. The most commonly affected organ system is the cardiovascular system, for which potential late effects of radiation therapy include pericardial effusion, pericarditis, and coronary artery disease, and late effects of chemotherapy include cardiomyopathy and congestive heart failure [34]. Possible late effects from both chemo- and radiation therapy include pulmonary fibrosis, neuropsychological deficits, bladder fibrosis, and cataracts. Organ systems affected by late effects specific to radiation therapy are the pituitary and thyroid systems, and that unique to chemotherapy is the peripheral nervous system.

Older cancer patients are at increased risk of cardiotoxicities, the most common of which is heart failure, due to chemotherapy and targeted therapy drugs [17]. Also, peripheral neuropathy due to late effects of chemotherapy is especially problematic among older survivors with gait and balance abnormalities [98]. Another example of this aging mimicry is the higher risk of osteoporosis among cancer survivors such as older breast cancer patients receiving aromatase inhibitors and prostate cancer survivors receiving androgen deprivation therapy. Other common signs of accelerated aging include fatigue, physical impairment, and memory loss. These late and potentially long-term effects of cancer treatment result in diminished organ function that often mimics that of normal aging [47, 99], often making it difficult to distinguish between the two. Such effects, while affecting quality of life for those who experience them, post greater risk on elderly patients who may already be at risk for infections, cognitive decline, and falls. In older cancer survivors, such changes can result in functional decline and possibly loss of independence and lead to reduced quality of life and possible earlier death. Therefore, survivorship management should include discussions and assessments of potential late effects of cancer treatment.

6.7 Impact on Survivorship Care Delivery for Older Patients

6.7.1 Interventions to Improve Status

Lifestyle behaviors, like maintaining a healthy diet and engaging in physical activity, change throughout the course of life. Older cancer survivors are more likely to be former smokers and are less likely to be aware of the impact of smoking on their overall health [100]. They are also more likely to perceive alcohol consumption as being beneficial to survival [100] and are less likely to meet physical activity goals [100–102]. In fact, on average, only 34–35% of older cancer survivors engage in sufficient levels of aerobic physical activity, compared to approximately 44% of their middle-aged counterparts [102]. Only about 10% of older cancer survivors meet goals for

both aerobic and muscle-strengthening physical activity guidelines [102]. When older cancer survivors struggle with one aspect of health behavior, like physical activity, they may also struggle with other aspects. Among older cancer survivors, physical function, physical activity, and diet quality are associated [103]. Thus, when providing lifestyle behavior counseling, older cancer survivors may have a unique nutritional and physical status that must be taken into consideration. Improving these behaviors, particularly by increasing exercise, can decrease fatigue and improve survivors' long-term health outcomes [104]. Therefore, appropriate lifestyle interventions could help older cancer survivors achieve and maintain optimal health.

Despite the need for lifestyle interventions, nearly one-quarter of long-term cancer survivors (e.g., those living 5 or more years beyond their cancer diagnosis) report that they never received lifestyle intervention or behavioral counseling from their physician [105]. Older cancer survivors, those aged 65 years or older, were even less likely to report discussing strategies to improve their health and diet with a physician [105]. Even when lifestyle counseling is provided, older survivors may be unable or reluctant to engage in moderate- or high-intensity activities [106]. Fortunately, even increasing light-intensity activities can reduce the decline of physical function in older cancer survivors [106]. Both telephone-based and home-based programs can help increase physical activity and adherence to exercise programs [107, 108]. Advocacy to increase patient engagement in physical activity programs may be warranted.

6.7.2 Care Coordination for Older Cancer Survivors

Healthcare for cancer survivors is complex, requiring the involvement of multiple disciplines [109]. It may be difficult to determine which healthcare professional is responsible for certain aspects of survivorship care. Among older cancer survivors, there may be increased complexity because of the presence and interaction between multiple chronic conditions and numerous medications to control them, changes in social support, and differing goals of therapy [109]. Survivorship care is a process that must continuously evolve to meet older adults' health needs [110]. In addition to providing behavioral change support and lifestyle interventions, survivorship healthcare needs might also include managing late- and long-term side effects of cancer treatment and monitoring for new or recurrent cancers [111]. Traditionally these types of healthcare needs are addressed by different disciplines, but there is no well-defined division of labor between different types of providers in the cancer survivorship arena, and this impacts the care that older survivors receive.

Depending on which clinical discipline is managing survivorship care (e.g., oncologists, primary care providers (PCP), or a combination of both), a cancer survivor might receive different types and intensity of care [112]. Primary care providers and cancer specialists may have different preferences for roles and responsibilities in delivering cancer survivorship care; they may also have differing knowledge and expertise [113, 114]. Similarly, cancer survivors may have unique views about the roles of their various healthcare providers [115]. Thus, various models of care have been proposed including primary care-based (e.g., a primary care provider or geriatrician takes ownership of survivorship care), specialty care-based (e.g., an oncologist or cancer specialist takes ownership of survivorship care), and shared care models (e.g., joint management of survivorship care) [116].

It has been proposed that a shared care model may be the best way to optimize care for older cancer survivors and ensure high-quality care [109]. Shared care allows for flexibility in providers' roles over time, depending on survivors' needs, and may be variable depending on time since diagnosis and completion of treatment, as well as recurrence status, and presence of other chronic conditions (Fig. 6.1). For a shared care model to be successful among older cancer survivors, there is a need for better integration of primary care, oncology, and geriatrics. A critical component of the shared care model is its focus

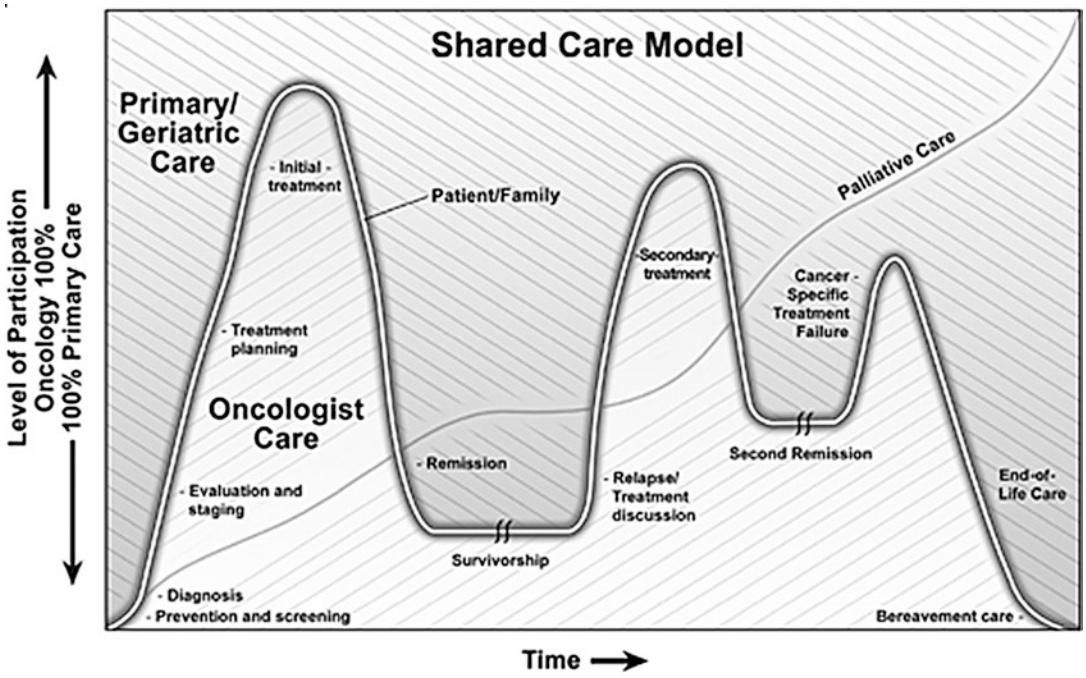

Fig. 6.1 A shared care model. (Reprinted with permission from Cohen [109], p. S300–S302)

on two-way, interactive communication between primary care and specialty care providers.

Effective shared care models will overcome traditional disciplinary communication barriers. For example, there are problems with delayed communication between primary care and cancer specialists and discrepancies between PCPs and cancer specialists regarding roles and expectations [116]. One way to improve communication is through innovative electronic health records that may facilitate multidisciplinary care coordination. There may also be a need for new disciplinary perspectives on shared roles in cancer survivorship care. While electronic tools can facilitate care coordination, it is also important to acknowledge the role of survivors, their family members, and caregivers. Survivors and their caregivers are often in an intermediary role between primary and specialty care. To maximize the effectiveness of shared care models, it is critical that patients, their family members, and caregivers be involved. Integrating patients' preferences and, when appropriate, that of their families is essential for ensuring quality, shared care.

Another model of cancer survivorship care coordination is risk-stratified care. In this model the frequency of encounters with cancer specialists is directly related to patients' clinical needs, including risk of recurrence and their late effects [117, 118]. For example, an older woman diagnosed with early stage breast cancer treated with excision alone might not need to see a medical oncologist for ongoing care. Instead, she could transition to being managed exclusively by her PCP unless she experiences a recurrence for which she will receive specialty care.

6.8 Survivorship Care Plans and Comprehensive Geriatric Assessments

According to the National Institute of Medicine (IOM), every survivor should receive an individualized survivorship care plan (SCP) that includes guidelines for monitoring and maintaining health [119]. Since the IOM's report, there have been a growing number of SCP templates and clinical

practice guidelines regarding SCP content and use. However, the quality of these guidelines is variable, and there is little guidance regarding how SCPs should be implemented [120]. Lack of implementation guidance may be one reason that, in the decade since the IOM report, few institutions have incorporated SCPs into clinical practice, and there is negligible evidence that SCPs improve patient-reported outcomes [121, 122].

Additionally, there has been very little work to evaluate the impact of SCPs in the context of older cancer survivors. Faul and colleagues enrolled older women with breast cancer (n = 328, aged 65 years and older) in a study and determined that only 35% of women received SCPs [123]. For each additional year of age, women had 5% lower odds of receiving an SCP, and this effect was significant. Aside from age, no other factor predicted whether the women received SCPs [123]. While there is little data about the effectiveness of SCPs generally or among older survivors, primary care providers and oncologists support SCPs and consider SCPs beneficial [124] but may have different views for how SCPs can be best used in different models of care [113].

Because older cancer survivors may have complex healthcare needs that require management from multiple specialists, anecdotally it seems SCPs might be particularly critical to facilitate care coordination in this population. Most cancer survivorship care plans include the names of the survivors' healthcare team, a treatment summary, and a follow-up care plan. Survivorship care plans are traditionally developed by the cancer care team and are intended to be consumed by the primary care team. In a model of shared care, survivorship care plans should be used to facilitate two-way communication between specialists and primary care. For older patients with complex care needs, a specialized survivorship care plan might be needed. Traditional survivorship care plans may omit information that is salient to older cancer survivors, such as atypical presentation of late effects of cancer treatment, exacerbation and acceleration of routine aging, inclusion of discussion of geriatric syndromes, and comorbid medical conditions and other related issues (Table 6.2). The survivorship care plan should be dynamic as patients' needs evolve.

Table 6.2 Potential components of survivorship care plan tailored for older adults

Oncology issues	Examples
Summary of cancer diagnosis and treatment regimens	Stage, initial treatment, and intent of treatment
Care team information	Cancer specialists, primary care providers, geriatricians
Ongoing risks from the cancer	Cancer recurrence and disease progression
Late effects of cancer and cancer treatment	Cardiotoxicity and osteoporosis
Prevention of recurrence and new cancers	Healthy diet, physical activity
Surveillance	Recommended follow-up of the current cancer, screening for new potential cancers
Sources of information	Age-appropriate and understandable references
Support groups and counseling services	Peer support programs, psychosocial support
Financial and insurance counseling services	Financial counseling and assistance programs, planning for cancer treatment costs
Contact information	When to seek care for symptoms/side effects and who to call
Geriatric wellness issues	Examples
Comorbidity and functional status	Review ongoing chronic disease management
Polypharmacy review	Medication reconciliation, adherence assessment
Healthy diet and physical activity recommendations	Prevention and management of chronic diseases, general wellness
Sleep	Sleep quality and duration
Social situation	Family and social support, living situation
Geriatric syndromes	Falls and incontinence

Note: Adapted from Salz et al. 2014 [132]

Comprehensive geriatric assessments provide complementary documentation on an older person's functional status, multiple morbid conditions, cognition, nutritional status, psychological state, and social support, as well as a review of the patient's medications [125]. It is important to note that multiple chronic conditions, functional status, and age are different aspects of the patient (Table 6.3) [126]. For example, an older cancer survivor with cancer may still have high func-

Table 6.3 Domains of comprehensive geriatric assessment

Domain	Potential measures [129, 131, 133]
Functional status	SF-36 Timed up and go Karnofsky performance status Activities of daily living
Comorbidity	Presence and severity of diseases and disorders OARS Physical Health Section Cumulative Illness Rating Scale for Geriatrics
Cognition	Mini-Mental State Examination Montreal Cognitive Assessment
Psychological	Mental Health Inventory Geriatric Depression Scale
Social functioning	Medical Outcomes Survey Social Activity Limitations subscale
Social support	Medical Outcomes Survey social support survey Seeman and Berkman Social Ties
Nutrition	Body mass index Percent of unintentional weight loss
Medications	Number of medications

tional status. Geriatric assessments can be valuable tools to detect functional impairments that would not otherwise be detected during a routine history and physical and to predict potential toxicities and influence treatment decisions [127]. Geriatric assessments can be used to guide interventions and to incorporate the principles of geriatrics into survivorship care plans [128]. One specific example of a geriatric assessment is the CALGB comprehensive geriatric assessment [129–131]. Using patient-reported information from the geriatrics assessment, multidisciplinary care teams can then develop a personalized survivorship care plan, track a survivor's progress, and adjust over time. In a shared care model, where a multidisciplinary team of providers follows survivors, this could have considerable impact.

6.9 Future Directions

Recent research in aging and cancer survivorship suggests the need to understand the unique characteristics and care needed by the older cancer population. A major hindrance in this area has been the underrepresentation of older cancer patients in cancer clinical trials, which inform many of the oncology guidelines. Clinical correlates often observed in geriatric cases such as cognitive impairment, multimorbidity, and polypharmacy are rarely considered in trials. This makes it difficult to extrapolate trial results to older patients with cancer. The National Comprehensive Cancer Network (NCCN), the European Organization for the Research and Treatment of Cancer (EORTC), and the International Society of Geriatrics Oncology (SIOG) have issued guidelines for managing older persons with cancer and broadly recommended the use of a comprehensive geriatric assessment and the age-specific guidelines for chemotherapy administration.

In general, future research should also focus on disentangling the late effects of cancer and its treatment on health from normal aging health changes. It is also important to understand mechanisms by which cancer detection and management can speed up functional decline in order to develop age-appropriate interventions and identify the subset of older patients most likely to benefit (e.g. pre-frailty). Clinical and research practice must ensure the application of appropriate tools for multiple chronic conditions, functional status, and psychosocial assessments for older cancer survivors. We must also provide the appropriate and currently preferred model of cancer survivorship care for older patients, including optimal medication management in survivors with polypharmacy. Guiding this work requires a fundamental consensus-based conceptual model of elderly cancer survivorship research [3].

As healthcare systems prepare for this burgeoning population and complex needs of older cancer survivors, it is important to incorporate more intentional integration between oncology and geriatrics. We must also ensure medical providers are equipped to manage this population, especially with the potential shortage of oncology providers [99] and therefore increased burden on primary care providers. With the increased focus on providing personalized cancer care, the two major components of which are the patient and the tumor, clinical trials and clinical practice must acknowledge and address the vast heteroge-

neity of older cancer survivors to provide the most appropriate tailored care. Now is the time to develop, research, and implement strategies to address issues unique to the aging population of cancer survivors before the "silver tsunami" occurs in the next few decades [6].

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Financial Hardship

7

Sarah E. Lewis, Maryam Doroudi, and K. Robin Yabroff

7.1 Introduction

Accumulating evidence indicates that cancer survivors are at a higher risk of experiencing financial hardship than persons without a history of cancer [1–3]. The effects of cancer include costs for care that have spiraled during the last decade [4–7]. The increased risk of developing additional cancers [8] and other chronic and acute conditions [9] contributes to a survivor's burden. Side effects and late effects of treatments that can limit the ability to work [10] can reduce household income. Work limitations might also reduce employment-based health insurance options, magnifying the financial impact. Fortunately, research addressing financial hardship among cancer survivors has also increased dramatically in the past decade [11], as financial hardship has become a prominent public health challenge.

Because of a growing population of older persons and increasing survival rates attributable to improvements in early detection and treatment, the number of cancer survivors is expected to grow from 15.5 million to 20.3 million during 2016–2026 in the United States [12]. The cost of cancer care is expected to also increase [13, 14]. During 1995–2013, the average launch price of a new therapeutic agent in oncology increased by an average of $8500/year (in 2015 dollars) [15]. New anticancer drugs can cost more than $60,000 (in 2015 dollars) for a month of treatment [16]. Additionally, for persons with health insurance, cost-sharing has increased through higher premiums, deductibles, copayments, coinsurance, and other out of pocket (OOP) expenses [17]. As an increasing number of survivors are likely to experience financial hardship following a cancer diagnosis, financial hardships will likely become even more common.

In this chapter, we describe a typology for evaluating financial hardship and provide an overview and illustrative examples of relevant research findings within each of the financial hardship domains. A framework for identifying factors that influence financial hardship is also presented. We then discuss measurement of financial hardship and the identification of key topics for future efforts in research and practice.

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7.2 Financial Hardship Typology

Because financial hardship among cancer survivors has been a prevailing public health topic among policy makers and consumers in recent years, multiple terms have emerged to name the adversity, including *financial toxicity*, *financial distress*, *financial stress*, *financial burden*, *economic burden*, and *economic hardship* [18–21]. For the purposes of this chapter, we use the term financial hardship, which comprises the basic domains of material conditions, psychological response, and coping behaviors [11], as illustrated in Fig. 7.1. Each domain has been consistently identified and evaluated in the United States [11] and in other countries [22].

Material conditions develop as a result of increased OOP expenses sustained from cancer diagnosis, its treatment, and lasting effects of treatment. Cancer survivors and their families might also face reduced income from limitations in the ability to work, frequently referred to as productivity loss [23].

Psychological responses include feelings of worry, distress, or concern about wages, meeting expenses because of cancer, its treatment, or lasting effects of treatment [24].

Coping behaviors describe what cancer survivors do to manage increased household expenditures and reduced household income, stress, worry, and the perception or expectation of material hardship [4].

As Fig. 7.1 illustrates, these domains overlap; however, they also can be mutually exclusive. For instance, a survivor might have very high material condition hardship by having high OOP spending on medical care, but might not have much worry about their financial situation, whereas another survivor might not have large OOP spending but could have significant worries affecting their psychological response to the cancer and noncancer financial demands.

Fig. 7.1 Domains of financial hardship: psychological response, material conditions, and coping behaviors. (From Altice et al. [11])

7.3 Material Conditions Research

Researchers typically measure material conditions as OOP spending for medical care and health care in general; productivity loss, including lost income, missed workdays [25], or inability to participate in usual activities [26]; and family members' personal leave from work [27]. High OOP costs and employment disruption can also result in asset depletion, trouble paying medical bills and other necessities (e.g., housing and food), medical debt, and bankruptcy for cancer survivors and their families [27–29].

7.3.1 OOP Spending

The majority of published research addressing material condition measures of financial hardship in the United States [11] and in other countries [22] is related to total OOP spending or OOP spending as a percentage of total household income. Cancer survivors typically report greater OOP expenditures than persons without a cancer history [30, 31]. For example, in a nationally representative sample selected from the Medical Expenditure Panel Survey (MEPS) in the United States, cancer survivors, ages 18–64 years, diagnosed within the past year reported $1107 in annual OOP spending, compared with $747 for previously diagnosed cancer survivors and $617 for those without a cancer history in the same age group. All estimates were

reported in 2013 US dollars [30]. Survivors are also more likely to report higher OOP burden (annual OOP spending on health care >20% of annual income) than persons without a cancer history [31–33]. In a study using the Medicare Current Beneficiary Survey, 28% of cancer survivors reported high OOP burden (≥20% of income spent on health care) compared with 16% for persons without a cancer history [32].

Some studies have addressed OOP spending among cancer survivors living outside of the United States [34–37]. Several studies have used the term *catastrophic spending* to categorize survivors' high OOP spending. Researchers typically measure material conditions, with thresholds varying from 30% of household income in studies in Southeast Asia [38, 39] to the top quartile of OOP spending in Canada [40]. For example, a Canadian study evaluated costs associated with patient time spent traveling to and from medical care and receiving care (i.e., time costs) and OOP spending in a cohort of prostate cancer survivors [37]. This study identified survivors through the Ontario Cancer Registry and conducted mail surveys and chart reviews to obtain time, OOP spending, and clinical characteristics. Although time costs (average $838/person in 2006 Canadian dollars; 95% CI, $442–$1233) and OOP spending (average $200/person; 95% CI, $109–$290) were not substantial in the Canadian cohort overall, OOP did represent ≥10% of income among some low-income survivors (average income of ≤$10,000). OOP estimates are not directly comparable with those in the United States' studies of differences in health care systems, study populations, means of collecting clinical characteristics, health care utilization, and study timing.

7.3.2 Productivity Loss

Productivity loss is typically measured as the inability to work or pursue usual activities, days lost from work or disability days, reduction in work hours, or days spent in bed. Productivity loss might be quantified directly from employment data [41] or estimated from a combination of days lost from work [30, 31] and median wages. Several studies have used data from the nationally representative MEPS to evaluate productivity loss among cancer survivors. Finkelstein et al. reported that, among employed persons, those receiving cancer care in the past year missed 22.3 more workdays per year than persons not receiving cancer treatment [42]. Employed cancer survivors reported cancer interfered with physical tasks (25%) and mental tasks (14%) required by the job [43]. Although much of the research regarding cancer and productivity loss has been focused on the United States, a study in Ireland estimated over €500 million (in 2009 euros) (approximately $600 million) were lost as a result of cancer-related premature mortality in 2009 [44] and €75 billion (in 2008 euros; approximately $90 billion) in Europe as a whole in 2008 [45].

7.3.3 Asset Depletion and Medical Debt

Multiple studies have reported asset depletion and medical debt for cancer survivors in the United States [46–56], although this information is rarely reported in relation to persons without a cancer history. Limited research has been conducted in relation to asset depletion and medical debt among cancer survivors outside the United States. Studies in the United States have reported that 30–80% of cancer survivors have used their savings to finance medical expenses [46–51], and 2–21% have borrowed money or have medical debt. Differences in prevalence ranges among studies might be attributed to response populations, from convenience samples to nationally representative samples, to the exact concept being measured [48, 52–55]. In a study of colon cancer survivors, mean acquired debt related to cancer treatment expenses for those already having debt was $26,860 [54]. To cope with expenses, cancer survivors have reported decreasing spending on leisure activities, food, clothing, housing, and utilities, and selling stocks, investments, possessions, or property [23, 26, 48, 50, 54].

7.3.4 Bankruptcy

A limited number of studies in the United States have addressed bankruptcy among cancer survivors [29, 49, 55]. A retrospective cohort study linked 15 years of data from the Western Washington SEER Cancer Registry with data from the U.S. Bankruptcy Court for the Western District of Washington and reported that cancer survivors were more likely to file for bankruptcy, compared with persons without a cancer history (hazard ratio [HR] = 2.65; $P < 0.05$) [29]. Additionally, among persons having cancer, the youngest age group (20–30 years) had higher rates of bankruptcy filings than the oldest age group (ages 80-90 years). The incidence rates for bankruptcy filing one year post-diagnosis was 10.06/1,000 person-years (versus 0.94/1,000 person-years, respectively. Thyroid cancer survivors had the highest HR (HR = 3.46, $P < 0.05$) of bankruptcy filing. This might be because thyroid cancer affects younger women more often than other cancers do, although information regarding relevant patient characteristics, such as socioeconomic status and health insurance, were not available in that study. A limited number of studies assess underlying causes for differences in financial hardship by cancer site.

A nationally representative study of cancer survivors in the United States indicated over 20% of respondents reported having material hardship of some kind (i.e., had to borrow money or go into debt, filed for bankruptcy, made other financial sacrifices) associated with cancer, its treatment, and late or lasting effects of treatment. The prevalence of any material financial hardship was higher among cancer survivors 18–64 years than those ≥65 years (28.4% versus 13.8%; $P < 0.01$). In the younger age group, being female, nonwhite and having changed employment because of cancer were associated with material hardship [55].

7.4 Psychological Response Research

Multiple studies conducted in the United States have examined prevalence of psychological financial hardship, including financial stress, worry about paying medical bills for cancer, or wage concerns (22.5%–63.8%) [49, 55, 56]. The wide range in prevalence reflects differences in samples; the 22.5% is from a nationally representative survey, and the 63.8% is from a web-based survey. Prevalence differences are also reflected in sample characteristics associated with psychological hardship across studies, differences in age distribution, cancer type, time since diagnosis, socioeconomic position, and health insurance. For example, younger cancer survivors are more likely to report psychological hardship than are older cancer survivors [49]. In a nationally representative sample, cancer survivors [49] ages 18–64 years were more likely to report being worried about paying for bills related to their cancer, its treatment, or the lasting and late effects of treatment than survivors ≥65 years (31.9% versus 14.7%; $P < 0.01$). Being uninsured, having lower household income, and receiving more recent cancer treatment were also associated with psychological hardship [55] . In a study conducted in Ireland, cancer-related financial stresses were associated with increased risk for depression [57].

7.5 Coping Behaviors Research

Problematic coping behaviors are often measured as medication nonadherence because of cost [58], or delaying or skipping care [21, 47, 59]. Several cross-sectional and longitudinal studies conducted in the United States evaluated the impact of the amount of prescription copayments for cancer drugs on survivors' adherence with drug therapy, as well as delays or skipping medication altogether [60–62]. One nationally representative cross-sectional study that compared persons with and without a history of cancer reported that 7.8% of cancer survivors (compared with 5.2% of the general U.S. population) forgo medical care because of cost, with 9.9% of cancer survivors (7.2% of the general population) not filing prescriptions because of cost. Being ≤65 years, as well as being Hispanic or black, were factors associated with being more likely to forgo prescription medications because of cost [60].

A longitudinal study examined the association between copayments for imatinib, an effective treatment for chronic myeloid leukemia, and medication adherence in survivors with chronic myeloid leukemia during 2002–2011 by using national private insurance claims [61]. Over the study period, monthly copayments for imatinib ranged $0–$4792 with a mean of $108 and median of $30. Patients in the highest quintile of monthly copayments for imatinib were more likely to discontinue imatinib (adjusted risk ratio [RR] = 1.70; 95% CI, 1.30–2.22) during the first 180 days of treatment, compared with patients in the lowest copayment quintile. Similarly, patients with the highest copayments for imatinib were more likely to be nonadherent to their imatinib therapy (adjusted RR = 1.42; 95% CI, 1.19–1.69). Another study examined the association between OOP costs and 12-month medication adherence to adjuvant endocrine therapy (AET) for women with stages I–III hormone receptor-positive breast cancer. The study used the National Cancer Institute's linked SEER-Medicare database, which links clinical information from cancer survivors' diagnosis from the SEER cancer registries with their Medicare claims data. Compared with breast cancer survivors in the lowest quintile of OOP costs for a 30-day supply of AET ($0–$2.65), those in the four higher cost categories (ranging $2.66– ≥$105) had lower adjusted odds of adherence to treatment ($P < 0.01$) [62]. Other studies examining copayments and adherence to care similarly found that those who faced higher levels of financial hardship (either self-reported or measured in dollars) in OOP costs were more likely to be nonadherent to chemotherapy, compared with cancer patients not facing this financial hardship [58, 63].

A 2017 study compared the changes in any prescription drug use for financial reasons between cancer survivors (those who reported being told they had cancer by a health care provider) and persons without a cancer history in the United States by using the 2011–2014 National Health Interview Survey (NHIS). Measures of changes in any prescription drug use for financial reasons in the past 12 months were skipping doses to save money, taking less to save money, delaying filing a prescription to save money, asking a doctor for a lower cost medication to save money, buying prescription drugs from another country to save money, and using alternative therapies to save money. Among persons aged ≥65 years, cancer survivors and those without a cancer history had similar rates of changes in prescription drug use for financial reasons. Among younger persons, aged 18–64 years, cancer survivors who were recently diagnosed or previously diagnosed with cancer were more likely to report any change in prescription drug use for financial reasons when compared with those without a cancer history (31.6%, 27.9%, and 21.4%, respectively) [64].

7.6 Framework for Identifying and Addressing Factors Associated with Financial Hardship

As previously noted, financial hardship and its typology domains are common among cancer survivors [18]. Evidence indicates that financial hardship is associated with increased risk for poor health outcomes [65]. The framework for conceptualizing factors associated with financial hardship and its consequences (Fig. 7.2) is adapted from the Social-Ecological Model (SEM) . SEM is a systems model used frequently to describe the multiple levels of a social system and the interactions between persons and their environment within the system that determine behaviors [66]. The framework has six hierarchical bands of influence: patient (cancer survivors), family, provider and provider teams, organizational, local community (state and regional organizations), and national and state policy. Additionally, the framework helps in identifying resources at individual-and systems-level and their intermediaries for potentially reducing financial hardship and improving health outcomes.

The innermost band of the SEM represents individual-level factors that can influence vulnerability to financial hardship following a cancer diagnosis. These factors include a person's

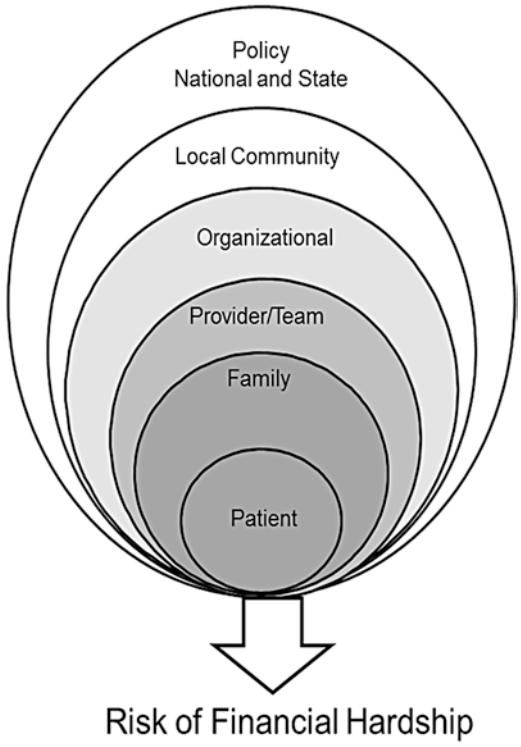

Fig. 7.2 Framework for Understanding and Addressing Multiple Influences on Financial Hardship. (Adapted from 'What are the Social Ecological Model (SEM), Communication for Development (C4D)?' UNICEF C4D, available at https://www.unicef.org/cbsc/files/Module_1_SEM-C4D.docx and the Centers for Disease Control and Prevention, the Social Ecological Model: A Framework for Prevention, available at http://www.cdc.gov/violenceprevention/overview/social-ecologicalmodel.html

preillness debt load, assets, illness-associated costs, ability to work, the presence or absence of health or disability insurance, and generosity of insurance coverage. These factors are common throughout the cancer survivorship trajectory. Other factors are specific to the cancer, including cancer site, stage at diagnosis, presence and type of metastases, types of treatment and treatment duration, as well as presence or absence of comorbidity [67].

The second band of the SEM represents interpersonal-level family (household) factors that influence a survivor's vulnerability to financial hardship. The household-related factors include wage-earner status of the affected household member, household's preillness debt load and assets, ability of household members to work, and incomes of other members of the household.

Physicians and other providers constitute the third band of the SEM. These health care providers pay considerable attention to the physical side effects of the therapies they prescribe; however, financial hardship from accumulating medical bills, distress, and related coping behaviors can also affect a survivor's wellbeing. Financial hardship experienced by cancer survivors can influence the timeliness of treatment, as well as adherence to treatment, ultimately affecting outcomes [59, 68]. Therefore, multidisciplinary interventions involving team members from clinical and support care and discussions on financial planning taking place parallel to the development of a treatment plan might reduce a cancer survivor's vulnerability to financial hardship. The University of Chicago's Cost of Cancer Care website has tools for patients to assess their financial hardship and provides information regarding cancer drugs that might be eligible for patient assistance programs [69]. Organizations, such as the Patient Advocate Foundation [70], the HealthWell Foundation [71], and the Cancer Financial Assistance Coalition [72], provide information regarding financial resources for patients and cancer survivors who need help with paying for their health care treatments.

Multiple studies have indicated that access to patient navigators, financial counselors, and social workers are effective in reducing treatment delays and treatment discontinuation among cancer patients [73, 74]. These professionals assist cancer survivors in removing logistical barriers to foundations, societies, and patient assistance programs to help with paying their medical and nonmedical bills. Although many cancer survivors report they want to discuss the costs of treatment with providers [75], many oncologists feel uncomfortable engaging in these discussions [76]. Moreover, oncologists might not be the member of the health care team best suited for this task. Professional societies, such as the American Society of Clinical Oncology, are currently in the process of developing protocols to assist providers in addressing the costs of cancer care and conducting cost-related conversations with their

patients [77]. Patient and provider communication challenges related to costs of cancer care is an active area of research [78, 79].

The fourth band of the SEM represents organizational-level factors that influence a cancer survivor's vulnerability to financial hardship. These factors include health care systems and their practice settings. Scarce research is available to address health care settings with respect to cancer survivors' financial hardship and the differences in hardship that might exist, depending on a facility's policies for charity care, uncompensated patient care, and insurance types that are accepted.

The fifth band of the SEM represents community-level factors that influence a cancer survivor's vulnerability to financial hardship. Activities at this level can positively influence vulnerability to financial hardship if survivors use resources and participate in community-level institutions, such as tribal health departments, county health departments, employer offerings, media information, and advocacy groups.

Successful treatment of cancer and survivorship care partially depend on access to high-quality health care services. In the United States, health insurance is key to health care access, which in most cases for working age persons, is private and provided by employers (group insurance) or purchased by persons individually from insurance companies. Governments also sponsor age- and income-based health-care programs, such as Medicare, primarily for individuals ≥65 years; or Medicaid, for individuals <65 years with very low incomes; or a supplemental payer after Medicare payments for individuals ≥65 years. Additionally, the type of health insurance a survivor has will determine what OOP costs the survivor pays throughout their cancer care. Therefore, concerns regarding insurance characteristics, such as the rates within a geographic area and the quality of insurance plans offered at the community-level, can serve as important determinants of a cancer survivor's vulnerability to financial hardship. Additionally, media and advocacy groups play a key role in raising the awareness and communicating the urgency of matters related to financial hardship for local and regional decision makers.

The sixth band of the SEM represents policy-level factors that can influence a survivor's vulnerability to financial hardship. Activities at this level might involve developing, interpreting, and implementing policies at federal, state, and local government agencies. One example is Medicaid expansion in the United States, which occurred as part of the 2010 Patient Protection and Affordable Care Act. Some states expanded coverage to all of their residents with household incomes below an established threshold, and others did not expand coverage to a similar population. A low-income cancer survivor in a nonexpansion state might have more difficulty obtaining medical insurance to cover the costs of treatment [80, 81]. A policy idea to help working cancer survivors be less vulnerable to financial hardship by Ramsey et al. is a government tax incentive for employers to offer supplemental insurance policies with fixed sums to cover household OOP expenses for the first year post-cancer diagnosis. The supplement would serve as a way of protecting survivors from incurring unaffordable amounts of debt from missing work because of cancer treatment and recovery [29].

7.7 Financial Hardship and Health Outcomes

Cancer survivors commonly experience multiple aspects of financial hardship, including material conditions, psychological response, and coping behaviors. Financial hardship is increasingly reported as a risk factor for poor health outcomes among survivors, including decrements in quality of life and increased risk for mortality (Fig. 7.3) [51, 82]. This section summarizes research findings related to adverse consequences of financial hardship among cancer survivors, including reduced quality of life and increased mortality risk.

7.7.1 Quality of Life Research

The associations between financial hardship, quality of life, and perceived quality of care were investigated in a population- and health care systems-based

Fig. 7.3 Cancer Diagnosis, Financial Hardship, and Health Outcomes (Adapted from Altice et al. [11])

cohort study [83]. Patient-reported health-related quality of life was measured by using the EuroQol five dimensions questionnaire, EQ-5D™ (EuroQol Research Foundation; Rotterdam, The Netherlands), a validated and widely used instrument that measures generic health status and is applicable to many health conditions and treatments, including cancer [83]. In the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) II study, among the surviving CanCORS survivors, one disease-free subcohort and one advanced disease subcohort were selected and resurveyed regarding their quality of life; the median duration of time since diagnosis was 7.3 years. Financial hardship was associated with lower health-related quality of life (adjusted beta = −0.06/burden category, 95% CI, −0.08 to −0.05), although not with lower perceived quality of care (OR = 1.09, 95% CI, 0.93–1.29) [51]. Advanced disease was associated with lower health-related quality of life (adjusted beta = −0.04, 95% CI, −0.08 to −0.01), however, no association was observed with advanced disease and financial hardship (OR = 1.25, 95% CI, 0.79–1.98).

An additional study using the same data reported that among survivors with lung or colorectal cancer diagnosis, financial hardship was negatively associated with health-related quality of life and positively associated with symptom burden, and vice versa. Those survivors with less than 2 months of financial reserves to maintain their current standard of living reported increased symptom burden, pain, and lower quality of life when compared with those who had more than 2 months of financial reserves [84].

Multiple cross-sectional studies have reported (from self-reports) that financial hardship among cancer survivors is associated with various consequences, including worse health-related quality of life [85], worse mental and physical health, less satisfaction with social activities and relationships [86], and increased depression and cancer related worries when compared with cancer survivors without financial hardship [87].

7.7.2 Mortality Risk Research

A minimal amount of research has addressed the association between financial hardship and mortality risk, and most of this work has been conducted in the United States. A retrospective cohort study comparing cancer survivors who did and did not file for bankruptcy in Western Washington's SEER Cancer Registry reported that filing for bankruptcy was associated with an increased risk for mortality (adjusted HR = 1.79, 95% CI, 1.64–1.96). Prostate (adjusted HR = 2.07, 95% CI, 1.5–62.74) and colorectal (adjusted HR = 2.47, 95% CI, 1.85–3.31) cancer survivors had the highest hazard ratios [82]. Findings were robust in multiple sensitivity analyses, including controlling for disease severity.

7.8 Financial Hardship Measures

Financial hardship, including material conditions, psychological responses, and coping behaviors, is increasingly recognized as a prominent concern for cancer survivors in the United States and other countries. Research concerning financial hardship is also increasing, but the lack of standardized, validated measurement tools for capturing financial hardship as a routine part of medical care [88] limits comparisons of research findings across different studies. The lack of widely adopted, gold standard measures and tools also limits comparisons across patient populations and countries. Ideally, multiple domains of financial hardship would be assessed to capture a more complete picture of the effects of financial hardship on a survivor's material, psychological and behavioral wellbeing. These assessments also would inform provider efforts to understand and address challenges for their patients and to tailor interventions to individual cancer survivors. Questions from existing instruments can be used to begin conversations in clinical settings.

A limited number of validated tools measuring financial hardship have been created but are relatively new and have yet to be widely adopted. Several studies have used the Personal Financial Wellness Scale [89], also called the InCharge Financial Distress/Financial Well-Being Scale [IFDFW Scale], which is arranged by the financial hardship domains I feel financially stressed in Table 7.1. Although the InCharge Scale is a valid and reliable instrument, it is not specific to financial hardship related to cancer and does not include items related to coping behaviors.

The COmprehensive Score for financial Toxicity (COST) measure is a new and validated survey, created by de Souza and colleagues in the academic cancer center setting to measure the financial effects of cancer diagnosis and treatment on cancer patients [90]. COST contains 11 questions, all of which contain response options on a Likert 5-option scale (ranging from not at all to a lot). Other researchers interested in financial hardship among patients have used the tool across various tumor types [47]. Multiple items in COST address the psychological response domain, with items such as 'I feel financially stressed' and 'I worry about the financial problems I will have in the future as a result of my illness or treatment.

Table 7.1 Financial hardship domains in the Personal Financial Wellness Scale

Domain	Text of question
Material	How often does this happen to you? You want to go out to eat, go to a movie, or do something else and *don't go because you can't afford to*?
	How frequently do you find yourself just getting by financially and living *paycheck to paycheck*?
Psychological	What do you feel is the *level* of your *financial stress today?*
	On the stair steps below, mark (with a circle) how *satisfied* you are with your *present financial situation.* The "1" at the bottom of the steps represents complete dissatisfaction. The "10" at the top of the stair steps represents complete satisfaction. The more dissatisfied you are, the lower the number you should circle. The more satisfied you are, the higher the number you should circle.
	How do you feel about your *current financial situation?*
	How often do you worry about being *able to meet* normal monthly living expenses?
	How confident are you that you could find the money to pay for a *financial emergency* that costs about *$1000*?
	How *stressed* do you feel about your personal finances *in general?*

Source: Prawitz et al. [89]

Continuing to quantify the health consequences of financial hardship on cancer survivors and their families and caregivers will be critical in documenting and addressing the full impact of financial hardship on cancer survivors. Additionally, several nationally representative surveys, including the National Health Interview Survey (NHIS) and the MEPS include questions related to financial hardship. Using items from these publically available surveys in future research allows for comparisons with nationally representative samples. The NHIS is an annual

household survey that conducts in-person interviews about a person's health status, health care access, and experiences with care [91]. The survey has a subset of questions about financial hardship for all adults, and cancer survivor questions are distinguishable from others.

Table 7.2 Financial hardship domains in the Medical Expenditure Panel Survey Experiences with Cancer

Domain	Text of question
Material	because of your cancer, its treatment, or the lasting effects of that treatment did you have any costs you had to pay out of your own pocket? Medical expenses Transportation Lodging Child care Home or respite care
	Have you or has anyone in your family had to borrow money or go into debt because of your cancer, its treatment, or the lasting effects of that treatment?
	Did you or your family ever file for bankruptcy because of your cancer, its treatment, or the lasting effects of that treatment?
	Please think about medical care visits for cancer, its treatment, or the lasting effects of that treatment. Have you ever been unable to cover your share of the cost of those visits?
	Have you or your family had to make any other kinds of financial sacrifices because of your cancer, its treatment, or the lasting effects of that treatment? Reduced spending on vacations or leisure activities Delayed large purchases (e.g., car) Reduced spending on basics (e.g., food and clothing) Use savings set aside for other purposes Made a change to living situation
Psychological	Have you ever worried about having to pay large medical bills related to your cancer?
	Have you ever worried about your family's financial stability because of your cancer, its treatment or lasting effects of that treatment?
	Have you ever been concerned about keeping your job and income, or that your earnings will be limited in the future because of your cancer?

Source: Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey. Available from: http://www.meps.ahrq.gov/mepsweb/

The MEPS is a 2-year panel survey that can be used cross-sectionally or longitudinally. Information regarding health, health care, employment, productivity loss, and health care spending, including OOP spending is included [92]. Because each MEPS panel is selected from the past year of the NHIS, it can be used in longitudinal evaluations of financial hardship for ≤3 years. In addition, the MEPS Experiences with Cancer survey contains a subset of questions that address financial hardship among cancer survivors. Table 7.2 lists the expanded version of questions fielded 2016–2018. Future studies can use these instruments in different settings to enhance the comparability of findings and focus on survivors across treatment settings (e.g., academic medical centers, private hospitals, public hospitals, etc.) to ensure that the financial hardships faced by cancer survivors across the geographic and income spectrum are being accurately measured.

7.9 Future Directions

As interest and research continues to grow in the area of financial hardship among cancer survivors, measuring and addressing psychological effects and coping behaviors, as well as material aspects are paramount. Systematic measurement across multiple levels and factors of financial hardship will be informative moving forward. For example, a better understanding of patient-level factors that might be associated with financial hardship, such as premorbid debt and assets, tumor type and disease stage, and family health are key. Similarly, at the patient level, having research that examines the effects of different types of health insurance and work-related benefits for illness or disability on a patient's risk for experiencing financial hardship is essential.

As demonstrated by the framework provided in this chapter, additional research can be conducted for multiple factors that might be associ-

ated with financial hardship. Research concerning the presence or absence of caregivers or concerning additional wage earners in the household should also help elucidate the complex consequences related to diagnosis and treatment of cancer. Gaining a better understanding of provider factors, such as provider specialties, whether the provider considers or counsels patients about costs of treatment, and alternative resources for treatment, might help to identify successful models of provider-patient interactions along the cancer care continuum that ultimately minimize the financial impact of treatment. Furthermore, research is needed to examine the influence of the type of care setting where a patient receives cancer treatment and risk for long-term financial hardship, particularly with mergers and consolidations of health care practices. These studies will address the concern that fewer sites of care in an area will lead to increased prices for health care services.

Much of the research concerning financial hardship is cross-sectional and cannot address causality. The National Cancer Institute's Physician Data Query evidence summary has outlined evidence gaps, including the development of interventions to address financial hardship domains (material conditions, psychological response, and coping behaviors) along with and the need for more standardized and validated measures, price transparency, and potential value-based payment models or alternative payment models [93].

Work reflecting on the tenth anniversary of the seminal Institute of Medicine report, From Cancer Patient to Cancer Survivor: Lost in Transition [94, 95], noted that the necessary, increased focus on financial toxicity aligns with one of the recommendations from the original report. As awareness and research in the importance of financial hardship among cancer survivors continue to grow, refining measures that can accurately and more systematically capture financial hardship is essential.

Note: The findings and conclusions in this chapter are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Part III

Problem Area: Symptoms

Fatigue

8

Karen M. Mustian, Po-Ju Lin, Kah Poh Loh, and Ian R. Kleckner

8.1 Definition of Cancer-Related Fatigue

Cancer-related fatigue (CRF) is a distressing, persistent, and subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [1, 2]. CRF is different from common physical or mental tiredness in that CRF is not relieved by sleep or rest, whereas general fatigue (i.e., physical or mental tiredness) is a transient inability to maintain optimal performance that is relieved by rest [3]. CRF negatively interferes with patients' ability to complete their cancer treatments and their ability to complete activities of daily living, and it reduces quality of life [3].

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8.2 Prevalence of Cancer-Related Fatigue

CRF can occur as a consequence of the cancer itself [4] or cancer treatment. It is the most commonly reported [5] and also the most distressing [6] side effect of cancer treatments including chemotherapy [7–9], radiation therapy [4, 10], or selected biologic modifiers [11]. As many as 40% of patients with cancer report CRF at the initial time of diagnosis [4], and the majority of patients experience CRF during the course of their treatment. Up to 90% [4, 10] of patients with a variety of cancer subtypes undergoing radiation therapy and up to 80% [7, 8] of those receiving chemotherapy experience CRF. While CRF will resolve for some survivors after completion of treatments, there are still approximately 30–40% of cancer survivors reported to have persistent CRF up to 10 years posttreatment [1, 3, 12–22]. In survivors of Hodgkin lymphoma, CRF has been shown to have a major impact on treatment outcomes and social reintegration [23].

8.3 Measurement of Cancer-Related Fatigue

Self-report assessment tools, also referred to as patient-reported outcome tools, are the most commonly used, reliable, and valid methods for

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both clinical and research measurement of CRF. There are many patient-reported instruments that can quantify CRF. A systematic review of 1453 published studies evaluating CRF instruments in patients with cancer and survivors [24] identified 37 studies and 40 instruments. The instruments were classified as three unidimensional and 37 multidimensional. These instruments vary by CRF dimensions, number of items, rating scales, types of cancer population studied, and psychometric properties. The validity and reliability were evaluated by internal consistency, test-retest reliability, and convergent validity. Of these 40 instruments, five instruments including:

1. Brief Fatigue Inventory (BFI) [25]
2. Cancer Fatigue Scale (CFS) [26]
3. Chinese CFS (C-CFS)
4. Functional Assessment of Cancer Therapy-Fatigue (FACT-F) [27], and
5. Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) [28]

have been optimally tested for validity and reliability with an internal consistency of 0.9 by Cronbach α coefficient and a concurrent validity ≥0.45 by Pearson correlation [24]. The type and the stage of cancer may affect CRF. Most of the CRF instruments were used in mixed cancer populations, and only a number of them used a homogenous cancer patient population, including the BFI [25], FACT-F [27], Fatigue Functional Impact Scale [29], MFSI-SF [28], Piper Fatigue Scale [30], Visual Analogue Scale (VAS) [31], and Wu Cancer Fatigue Scale [32].

Although the measurement of CRF is not universally standardized, some instruments are more commonly used than others, as listed in Table 8.1. The authors of a systematic review review suggest use of a simple unidimensional measure that includes a rating of severity (such as the FACT-F and VAS) as an initial step for identifying the presence of CRF among survivors. If CRF is present, a multidimensional instrument can be considered to further identify the most problematic domain(s) of CRF. Oncologists and clinicians then can prescribe the optimal treatment specifically targeting the problematic domains for patients at early stages of cancer and survivors who have completed primary treatments but are still receiving hormone therapies or biologics. The authors of the systematic review recommended using BFI to evaluate CRF in patients with advanced cancer undergoing palliative treatment given the short length of the questionnaire (fewer than 10 items) and its optimal psychometric properties [24]. In addition, BFI is sensitive when measuring change of CRF over time. The three items related to fatigue included in the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 [33] have also been used among patients with advanced cancer [24] and validated with good test-retest reliability [34].

8.4 Possible Mechanisms Associated with Cancer-Related Fatigue

A number of mechanisms associated with the development of CRF have been proposed in recent decades. Some of these include (1) anemia, (2) circadian rhythm disruption, (3) stress and cytokine dysregulation, (4) psychological distress, (5) pain and neuroimmunologic changes, (6) cardiovascular and physical dysfunction, and (7) energy, nutritional deficits, and imbalance [42–44]. Of these potential mechanisms, cytokine dysregulation has been the most studied to date. Research has shown that cancer may activate pro-inflammatory cytokines, such as interleukin-6 (IL-6), and markers of inflammation, such as C-reactive protein (CRP), resulting in the development of CRF prior to cancer treatment initiation [45–50]. In addition, cancer treatments continue to prolong activation of pro-inflammatory cytokines during treatment [45, 51] and after treatment completion [43].

The use of radiation therapy and chemotherapy is also associated with increased inflammation (e.g., CRP, IL-1 receptor antagonist, IL-6). Patients with breast and prostate cancer have been shown to have elevated levels of CRP and IL-1 receptor antagonist [52]. In another sample of 53 patients with breast cancer receiving chemotherapy, serum IL-6 was found to be

Table 8.1 Commonly used instruments for measurement of cancer-related fatigue

Instruments	Dimensions	Number of items	Scales	Evaluation period	Description
Unidimensional					
EORTC QLQ C30 [33]	Severity of fatigue	3	4-point (1–4) Likert	Past week	Three items are: "Did you need to rest?" "Have you felt weak?" and "Were you tired?"
FACT-F [27]	Severity of fatigue	13	5-point (0–4) Likert	Past week	A 13-item stand-alone statement as a part of FACT is used to assess the severity of fatigue
POMS-F [35]	Severity of fatigue	7	5-point (0–4) Likert	Past week and right now	A seven-item fatigue subscale of POMS assesses the severity of recent fatigue
VAS [36]	Severity of fatigue	1	Analogue	Current	Patients mark fatigue severity between a linear scale with end points between "I am not tired at all" and "I am totally exhausted"
Multidimensional					
BFI [25]	Severity and interference of fatigue	9	11-point (0–10) Likert	Past 24 h	Three items assess the severity of fatigue "now," "usually," and at its "worst." Six items assess the interference of fatigue on daily function, including general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life
CFS [26]	Physical, affective, and cognitive fatigue	15	5-point (1–5) Likert	Current	Seven items assess physical fatigue, and four items assess affective and cognitive fatigue. Total score is the sum of the three subscales. CFS is easy and short and can be completed by patients with advanced cancer
CFQ [37]	Physical and mental fatigue	14	4-point (0–3) Likert	Current	Eight items assess physical symptoms, and the remaining six items assess mental fatigue symptoms. CFQ is a brief, easy to administer instrument
FSI [38]	Intensity, duration, and interference of fatigue	13	11-point (0–10) Likert	Past week, current	Four items assess the severity of fatigue at its "most," "least," and "average" during the past week and "right now." Seven items assess the interference of fatigue on daily function, including general activity, ability to perform daily-living activities, normal work, ability to concentrate, relations with other people, enjoyment of life, and mood. Two items assess the duration and intensity of fatigue
MFI-20 [39]	Cognitive, physical, and emotional fatigue, reduced activity, reduced motivation	20	5-point (1–5) Likert	Current	Four items are presented for each dimension, two of which indicate fatigue, and the remaining two are contradictory of fatigue
MFSI-SF [40]	General, physical, mental, and emotional fatigue, vigor	30	5-point (0–4) Likert	Past week	Six items are included in each dimension. Total MFSI score is calculated as (general + physical + mental + emotional) – vigor
Piper Fatigue Scale [30]	Behavioral/severity of fatigue, affective meaning, sensory, cognitive/mood	22	11-point (0–10) Likert	Now or today	Six items assess behavioral/severity, five items each assess affective meaning and sensory, and six items assess cognitive/mood
SCFS-6 [41]	Physical and perceptual fatigue	6	5-point (1–5) Likert	Past 2–3 days	SCFS-6 was developed from the original SCFS with 28 items. Patients rate six items that describe feelings associated with fatigue from 1 = "not at all" to 5 = "extremely"

EORTC QLQ C30 European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30, *FACT-F* Functional Assessment of Cancer Therapy-Fatigue subscale, *POMS-F* Profile of Mood Sates-Fatigue subscale, *VAS* Visual Analogue Scale, *BFI* Brief Fatigue Inventory, *CFS* Cancer Fatigue Scale, *CFQ* Chalder Fatigue Scale, *FSI* Fatigue Symptom Inventory, *MFI-20* Multidimensional Fatigue Inventory-20 items, *MFSI-SF* Multidimensional Fatigue Symptom Inventory-Short Form, *SCFS-6* Schwartz Cancer Fatigue Scale-6

increased after treatment [53]. These inflammatory markers are positively associated with increased self-reported CRF [47, 50, 53–62]. Clevenger et al. [47] showed that in 136 women with ovarian cancer, higher levels of plasma IL-6 was associated with greater CRF prior to surgery. Pertl et al. [50] also reported a positive association of plasma CRP levels and self-reported CRF in 61 patients with breast cancer prior to initiation of chemotherapy. In 103 breast cancer survivors, elevated plasma soluble tumor necrosis factor receptor type II (sTNFRII), which is a downstream marker of TNF activity, was associated with persistence of CRF one month after treatment [58]. Breast cancer survivors who received chemotherapy had higher levels of CRF and sTNFRII level compared to those who did not receive chemotherapy. Other studies also reported the positive associations of CRF with CRP [56, 60, 61], IL-6 [62], and IL-1 receptor antagonist [60] in long-term cancer survivors who received any modality of treatment. In addition, cancer survivors with persistent CRF showed increased expression of genes encoding pro-inflammatory cytokines [57, 59]. However, the association of CRF and inflammation markers is not consistent. CRP and IL-1 receptor antagonist were not found in association with CRF in women newly diagnosed with breast cancer [48] or shortly after primary treatment [58]. Also, IL-6 was not correlated with CRF in breast cancer patients prior to chemotherapy [50].

The dysregulation of pro-inflammatory cytokines may influence CRF directly or indirectly. Disruption can occur via the hypothalamic-pituitary-adrenal axis (HPA axis), autonomic nervous system, and circadian rhythm modulation. The HPA axis controls the secretion of cortisol during stress. Bower et al. [63] reported that breast cancer survivors without CRF responded to stress with an increased cortisol level, while those with CRF demonstrated a blunted cortisol response to stress.

Circulating cortisol concentration also changes throughout the day based on the circadian rhythm [64]. In a healthy adult, the blood level of cortisol quickly increases after awakening and reaches a peak level 30 min after waking up. This is followed by a decline throughout the day, and the level reaches its minimum at night during sleep [64–66].

However, a disrupted circadian rhythm was observed in patients with cancer irrespective of stage or treatment. The disrupted circadian rhythm may be associated with the occurrence of CRF [64, 67, 68]. Studies have shown that patients with cancer and persistent CRF had an altered diurnal cortisol slope and elevated evening cortisol levels during adjuvant therapy [69] and after cancer treatment [70].

CRF is also associated with elevated norepinephrine and lower heart rate variability in breast cancer survivors at least two to three months post-treatment [71, 72]. However, these findings are not conclusive, and more studies are warranted to fully understand the relationship between the autonomic nervous system and CRF.

8.5 Treatment of Cancer-Related Fatigue

Many randomized clinical trials have attempted to treat CRF using interventions such as exercise, psychological therapies, mind-body approaches, pharmacological interventions, and others [43]. In a recent meta-analysis of 113 randomized clinical trials using exercise, psychological, the combination of exercise and psychological, or pharmacological interventions to treat CRF in adult cancer patients and survivors, Mustian et al. [73] demonstrated that exercise, psychological, and the combination of exercise and psychological interventions reduced CRF during and after treatment, whereas pharmacological interventions alone did not reduce CRF. We elaborate on different interventions in the following sections.

8.5.1 Exercise

Over a dozen systematic reviews and meta-analyses have been conducted to assess the effect of exercise on CRF in adult patients [74–86], children, and adolescents with cancer [87–89] during

and after cancer treatment. Overall, supervised aerobic and/or the combination of aerobic and resistance exercise with or without stretching have been found to be effective in reducing CRF, particularly in the domains of general and physical fatigue [76]. The positive impact of exercise on CRF was shown in adult patients with cancer during [75, 76, 82, 85] and after treatment [77, 78, 82, 84]. Given that multiple studies demonstrated the benefits of exercise, the American College of Sports Medicine (ACSM) recommends that patients with cancer and cancer survivors start low and increase to 150 min weekly of moderate intensity or 75 min of vigorous intensity aerobic exercise accompanied by 20–30 min of strength training across all the major muscle groups two to three times with daily stretching [90]. Despite this recommendation, an estimated 70% of cancer survivors do not meet the standard established by the ACSM physical activity guideline [91].

The appropriate exercise mode, intensity, frequency, and duration need to be carefully considered, and an individualized exercise prescription is strongly recommended when discussing exercise with cancer populations. Mustian et al. [92] suggested that exercise prescriptions for cancer patients and survivors should be individualized and tailored based on the individual's health status, disease trajectory, previous and/or current treatment, symptom burden, current fitness level, past and present exercise participation, and individual preferences to ensure that the exercise is safe and effective. This is illustrated by Tian et al. [77] who reported that supervised aerobic exercise for 50 min/session, two sessions/week for eight weeks, had a moderate effect on CRF, while the same exercise only had a small effect on CRF when it was performed using shorter sessions occurring more frequently: 20–30 min/session, three sessions/week. Clinicians should also consider barriers that cancer patients face in completing exercise and should consider the use of new technologies in improving and tracking exercise adherence [93]. In children and adolescents with cancer, the effects of exercise on CRF are not consistent and are likely due to the lack of rigorous studies [87, 88].

8.5.2 Psychosocial Therapy

Some meta-analyses have demonstrated that psychosocial therapy has small to moderate effect sizes on CRF reduction relative to a control [73, 94–96]. For example, three randomized controlled trials of psychosocial interventions in patients with breast cancer undergoing chemotherapy or radiation therapy who received a three-session individualized CRF education and support program showed improvement in CRF compared to controls [97–99]. These benefits were also seen in the posttreatment period. One of the largest trials, The Moving Beyond Cancer Trial, with 418 breast cancer patients who recently ($\leq$ 6 weeks) completed surgery, showed that a 23-min psychoeducational video, which addresses reentry challenges in physical health, emotional well-being, interpersonal relations, and life perspectives, significantly improved CRF six months after the intervention compared to the control group [100].

8.5.3 Mind-Body Approaches

In recent years, mind-body approaches such as yoga, acupuncture, and meditation have been commonly studied in adult cancer populations for management of CRF [101–116]. Some studies evaluated the effects of yoga on CRF in patients with cancer receiving chemotherapy or radiotherapy [105, 108, 109, 111, 113, 114]; others investigated the efficacy of yoga on CRF in cancer survivors after the completion of cancer treatment [101–104, 106, 107, 109–112, 115, 116]. Eight studies showed that yoga significantly reduced CRF at the end or months after the intervention has been completed compared to the control group, which was usual cancer care [101, 104, 106, 115, 116] or a health education intervention [102, 103, 114]. However, six studies did not find a group difference for the effects of the mind-body intervention on CRF [108–113]. These studies are heterogeneous in terms of the type, duration, intensity, frequency, and length of the yoga intervention. Taken together, studies that

showed benefits of yoga on CRF reduction suggest that gentle yoga performed in 60- to 120-min sessions, at low to moderate intensity, one to three times per week over a period of four to 12 weeks, may improve CRF in patients with cancer and survivors [117].

In another two studies that evaluated the effect of acupuncture on CRF in 429 patients with a variety of cancer subtypes, authors found patients who received acupuncture had significantly improved CRF compared to patients in the usual care group [118, 119]. However, when acupuncture was compared to sham acupuncture, no difference in CRF was noted [120]. While a number of systematic reviews of acupuncture and its effect on CRF have been conducted [121–125], results are inconsistent. More rigorous randomized control trials are needed.

8.5.4 Pharmacological Interventions

There have been over 14 randomized trials examining pharmacological interventions, but the evidence supporting their ability to treat CRF among cancer survivors is limited [73]. Existing studies showed mixed findings, often did not use rigorous trial designs, and included only small sample sizes [126]. Modafinil and methylphenidate were most commonly studied. In a randomized controlled trial of 631 patients with mixed cancer types undergoing chemotherapy, only those with severe CRF (score ≥ 7 on the scale of 0–10 in the BFI item 3 "What is your worst level of CRF during the past week?") benefited from modafinil [127]. In contrast, another randomized controlled trial of 208 patients with non-small cell lung cancer showed that patients who received modafinil demonstrated no improvement in CRF [128]. For methylphenidate, a meta-analysis of five studies [129] suggested possible benefits in three studies [130–132] where CRF was evaluated by Functional Assessment for Chronic Illness Therapy-Fatigue (FACIT-F) but not in the other two studies [133, 134] where CRF was measured by BFI. In addition, methylphenidate may be associated with vertigo, anxiety, anorexia, and nausea [129]. Given the limited evidence, most guidelines from professional societies recommend using pharmacologic interventions after ruling out other causes of fatigue or if behavioral interventions have failed.

8.6 Clinical Practice Guidelines for Cancer-Related Fatigue

The American Society of Clinical Oncology, National Comprehensive Cancer Network, and Pan-Canadian Clinical Practice Guidelines for clinicians and health professionals are summarized in Table 8.2. Each of these guidelines includes recommendations on screening, comprehensive and focused assessment, and treatment options.

8.6.1 Screening

All healthcare providers should routinely screen for the presence of CRF at the time of initial diagnosis and on subsequent visits, including after the completion of primary treatment. Screening should be performed and documented using a quantitative or semiquantitative, valid, and reliable tool (see Table 8.1) to assess CRF (e.g., asking patients "How would you rate your fatigue on a sale of 0–10 over the past seven days?" from 0 to 10 as 0 = no fatigue and 10 = worse fatigue or using a rating of mild, moderate, or severe).

8.6.2 Comprehensive and Focused Assessment

History and physical examination, including fatigue history (onset, pattern, duration, changes over time), disease status (progression, recurrence), medication/supplement usage and side effects, social support, and economic status should be incorporated during these visits. Laboratory evaluation, such as complete blood count with differential and comprehensive metabolic panel, should be considered depending on the presence, onset, and severity of CRF as well

Table 8.2 Current screening, assessment, and treatment clinical practice guidelines for cancer-related fatigue

	American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Adaptation [3]	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology- Cancer-Related Fatigue (version 2.2017, NCCN.org) [1]	NCCN Clinical Practice Guidelines® in Oncology-Survivorship (version 2.2017) [135]	Pan-Canadian Guideline (version 2.2015) [2]
Clinical question	What are the optimal screening, assessment, and treatment approaches in the management of adult cancer survivors who are experiencing symptoms of CRF after completion of primary treatment?	N/A	N/A	What are the optimum assessment parameters following screening and effective interventions for management of CRF in adults with cancer who are identified as experiencing symptoms of CRF or tiredness on the Edmonton Symptom Assessment System (ESAS)?
Definition of cancer-related fatigue (CRF)	Adopted NCCN definition of CRF	CRF is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.	Same as NCCN definition of CRF; however, these guidelines are focused on CRF after the completion of cancer treatment and/or inpatients who are in clinical remission.	Adopted NCCN definition of CRF
Screening	All healthcare providers should routinely screen for the presence of CRF from the point of diagnosis onward, including after completion of primary treatment. All patients should be screened for CRF as clinically indicated and at least annually. Screening should be performed and documented using a quantitative or semiquantitative assessment.	Screen every patient for the presence or absence of CRF If CRF is present, a quantitative or semiquantitative assessment should be performed and documented. For example, fatigue rating scale: 0 = no fatigue and 10 = worst fatigue; 1–3 = mild, 4–6 = moderate, 7–10 severe fatigue. If the screening process determines that CRF is absent or at a mild level, the patient and family should receive education and common management strategies for CRF. Periodic rescreening and reevaluation are recommended. Inpatients should be screened daily, and outpatients should be screened at a subsequent routine and follow-up visits. It should be emphasized that survivors or patients who have completed treatment must still be monitored for CRF because CRF may exist beyond the period of active treatment.	Sample survivorship care survey: Do you feel persistent CRF despite a good night's rest? Yes/no Does CRF interfere with your usual activities? Yes/no How would you rate your CRF on a scale of 0 (none) to 10 (extreme) over the past month? 0–10	All healthcare providers should routinely screen for the presence of CRF from the point of diagnosis onward. All patients should be screened for CRF at their initial cancer clinic visit, at appropriate intervals (e.g., daily for inpatients, routine and follow-up visits for outpatients, and self-monitoring for those posttreatment) and as clinically indicated, especially with changes in disease status. Screen with a valid and reliable tool that includes reportable scores (dimensions) that are clinically meaningful and have established cut-offs (e.g., asking patients "How would you rate your fatigue on a sale of 0–10 over the past 7 days" with ESAS scale from 0–10 as 0 = no fatigue, 10 = worse fatigue. The cut-off scores are 0–3 none to mild, 4–6 moderate, and 7–10 severe CRF. For patients who are unable to assign a numeric value to rate their CRF, a rating of mild, moderate, or severe may be used.) ESAS is a valid and reliable assessment tool to assess severity for nine common cancer symptoms, including pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath.

(continued)

Table 8.2 (continued)

	American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Adaptation [3]	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology- Cancer-Related Fatigue (version 2.2017, NCCN.org) [1]	NCCN Clinical Practice Guidelines® in Oncology-Survivorship (version 2.2017) [134]	Pan-Canadian Guideline (version 2.2015) [2]
Comprehensive and focused assessment	**History and physical** Perform a focused CRF history Evaluate disease status Assess treatable contributing factors As a shared responsibility, the clinical team must decide when referral to an appropriately trained professional (e.g., cardiologist, endocrinologist, mental health professional, internist) is needed. **Laboratory evaluation** Consider performing laboratory evaluation based on the presence of other symptoms and onset and severity of CRF	When CRF is rated as moderate to severe with a score 4–10, a more focused history and physical examination should be conducted. **Focused history** Disease status and treatment Consider recurrence and/or progression Prescription medications, over-the-counter drugs, and supplements Review of systems In-depth CRF history Onset, pattern, duration Change over time Associated or alleviating factors Interference with function Social support status/availability of caregivers Economic status and resources for obtaining tangible support **Assessment of treatable contributing factors** Pain Emotional distress Depression Anxiety Anemia Sleep disturbance/poor sleep hygiene (e.g., insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome) Nutritional deficits/imbalance Weight/caloric intake changes Fluid electrolyte imbalance: sodium, potassium, calcium, magnesium Decreased functional status Physical activity level Deconditioning Medications/side effects (e.g., sedation) Comorbidities Alcohol/substance abuse Cardiac dysfunction Endocrine dysfunction (e.g., hot flashes, hypothyroidism, hypogonadism, adrenal insufficiency)	Primary evaluation fatigue score: moderate or severe (4–10) **History and physical** Focused CRF history Onset, pattern, duration Change over time Associated or alleviating factors Interference with function Evaluation disease status Evaluate risk of recurrence based on stage, pathologic factors, and treatment history Perform review of systems to determine if other symptoms substantiate suspicion for recurrence Assessment of treatable contributing factors Comorbidities Alcohol/substance abuse Cardiac dysfunction Endocrine dysfunction (e.g., hypothyroidism, hypogonadism, adrenal insufficiency) Pulmonary dysfunction Renal dysfunction Anemia Arthritis Prescribed or OTC medications (e.g., sleep aids, pain medications, antiemetics) Emotional distress (screen for anxiety and depression) Sleep disturbances (e.g., insomnia, sleep apnea, vasomotor symptoms, restless leg syndrome) Pain Nutritional issues Weight/caloric intake changes Deconditioning/loss of muscle mass **Laboratory evaluation** Consider performing laboratory evaluation based on presence of other symptoms, onset, and severity of CRF CBC with differential Compare end-of-treatment hemoglobin/hematocrit with current values Assess other cell lines (WBC and platelets) Comprehensive metabolic panel Assess electrolytes	Screen for CRF and if moderate or severe CRF is detected through screening (ESAS tiredness greater than 4); individuals should have a comprehensive and focused assessment to identify the nature and extent of the CRF symptoms. Medical and substance-induced causes of CRF should be ruled out (e.g., anemia, infection, nutrition, deficiencies, medication or treatment side effects). Assessments should be a shared responsibility of the clinical team, with designation of those who are expected to conduct assessments based on scope of practice. Assessment should include a history of CRF (e.g., disease status, pretreatment activity levels, CRF onset, pattern, duration, changes over time, interference with function and daily living), contributing risk factors (e.g., depression, anemia, pain, nausea, sleep disturbance, comorbidities), a physical exam, a review of symptoms, and a self-assessment of causes contributing to CRF. Promote open communication among the patient, family, and the clinical team to facilitate discussions about the experience of CRF and its effects on daily functioning. As a shared responsibility, the clinical team must decide when referral to an appropriately trained professional is needed (e.g., all patients with an ESAS score in the severe range, with certain accompanying factors or symptoms, or a cut-off score identified using valid and reliable tools for assessment of symptoms of CRF.

		Gastrointestinal dysfunction Hepatic dysfunction Infection Neurologic dysfunction Pulmonary dysfunction Renal dysfunction	Assess hepatic and renal function Endocrine evaluation TSH, especially in patients who have received prior head/neck, torso, or breast radiation Consider more comprehensive evaluation or referral to specialist if other symptoms present Cortisol stimulation test, if history of prolonged steroid use **Other diagnostic testing** Consider radiologic assessment only if there is a high risk of disease recurrence or if accompanying signs and symptoms suggest presence of metastatic disease Consider cardiac testing (e.g., echocardiogram) for patients treated with an anthracycline, trastuzumab, bevacizumab, other VEGF- or HER2-targeted therapy, or other therapy known to cause cardiac dysfunction Chest x-ray and oxygen saturation testing for pulmonary complaints (refer to a pulmonologist for pulmonary complaints)	
Treatment and care options	**Education and counseling** All patients should be offered specific education about CRF after treatment (e.g., information about the difference between normal and CRF, persistence of CRF after treatment, and causes and contributing factors). Patients should be offered advice on general strategies that help manage CRF. If treated for CRF, patients should be observed and reevaluated on a regular basis to determine whether treatment is effective or needs to be reassessed. **Contributing factors** Address all medical and treatable contributing factors first (e.g., pain, depression, anxiety, emotional distress, sleep disturbance, nutritional deficit, activity level, anemia, medication adverse effects, and comorbidities). **Physical activity** Initiating/maintaining adequate levels of physical activity can reduce CRF in posttreatment survivors. Actively encourage all patients to engage in a moderate level of physical activity after cancer treatment (e.g., 150 min/week of moderate aerobic exercise, such as fast walking, cycling, or swimming, with an additional 2–3 strength training sessions/week, such as weight lifting, unless contraindicated). Walking programs are generally safe for most cancer survivors; the ACSM recommends that cancer survivors can begin this type of program after consulting with their physicians but without any formal exercise testing, such as stress test.	**Patient/family education and counseling** Information about known pattern of CRF during and following treatment **General strategies for management of CRF** Monitor CRF levels Energy conservation Set priorities and realistic expectations Pace Schedule activities at times of peak energy Limit naps to <1 hour to not interfere with night-time sleep quality Structured daily routine Attend to one activity at a time Use distraction (e.g., games, music, reading, socializing) Find meaning in current situation Emphasis on meaningful interactions Promote dignity of patient **Non-pharmacologic interventions** Physical activity Maintain optimal level of activity Consider initiation of exercise program of both endurance and resistance exercise Consider referral to rehabilitation physical therapy, occupational therapy, physical medicine Caution: late effects of treatment (e.g., cardiomyopathy)	**Treat contributing factors** Medication/side effects Pain Emotional distress Anemia Treat iron, B12, and folate deficiency, if present Consider referral/further evaluation for anemia or cytopenias Sleep disturbance Nutritional deficit/imbalance Comorbidities **Patient/family education and counseling** Provide information about patterns of CRF during and after treatment Self-monitoring of CRF levels Energy conservation Set priorities Pace Schedule activities at times of peak energy **Physical activity** Maintain adequate levels of physical activity Survivors at higher risk of injury (e.g., those living with neuropathy, cardiomyopathy, lymphedema, or other long-term effects of therapy or other comorbidities) should be referred to a physical therapist or exercise specialist Mark use of local resources to help patients increase exercise	Address all medical and treatable contributing factors first (e.g., pain, depression, anxiety, emotional distress, sleep disturbance, nutritional deficit, activity level, anemia, medication adverse effects, and comorbidities). Actively encourage all patients to engage in a moderate level of physical activity during and after cancer treatment (e.g., 30 min/week of moderate intensity activity most days) unless contraindicated. Moderate activity includes aerobic (e.g., fast walking, cycling, or swimming) and resistance training (e.g., weights). Additional non-pharmacologic interventions include nutrition consultation, optimizing sleep quality, psychosocial interventions to improve coping with CRF (e.g., cognitive behavioral therapy, stress management, or support groups), relaxation, massage, and attention restoring therapy (e.g., exposure to natural environments). For patients on active treatment or on long-term follow-up posttreatment who have moderate to severe CRF, consider referral to rehabilitation (e.g., physical or occupational therapy and physical medicine).

(continued)

Table 8.2 (continued)

	American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Adaptation [3]	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology- Cancer-Related Fatigue (version 2.2017, NCCN.org) [1]	NCCN Clinical Practice Guidelines® in Oncology-Survivorship (version 2.2017) [134]	Pan-Canadian Guideline (version 2.2015) [2]
	Survivors at higher risk of injury (e.g., those living with neuropathy, cardiomyopathy, or other long-term effects of therapy) and patients with severe CRF interfering with function should be referred to a physical therapist or exercise specialist. Breast cancer survivors with lymphedema should also consider meeting with an exercise specialist before initiating upper-body strength training. **Psychosocial interventions** Cognitive behavioral therapy/behavioral therapy can reduce CRF in posttreatment survivors. Psychoeducational therapies/educational therapies can reduce CRF in posttreatment survivors. Survivors should be referred to psychosocial service providers who specialize in cancer and are trained to deliver empirically based interventions. Psychosocial resources that address CRF may also be available through the NCI and other organizations **Mind-body interventions** Some evidence showed that mindfulness-based approaches such as yoga and acupuncture can reduce CRF in cancer survivors. Additional research, particularly in the posttreatment population, is needed for biofield therapies (touch therapy), massage, music therapy, relaxation, reiki, and qigong. Survivors should be referred to practitioners who specialize in cancer and who use protocols that have been empirically validated in cancer survivors. **Pharmacologic interventions** Evidence suggests that psychostimulants (e.g., methylphenidate) and other wakefulness agents (e.g., modafinil) can effectively manage CRF in patients with advanced disease or those receiving active treatment. However, there is limited evidence of their effectiveness in reducing CRF in patients who have completed primary treatment and are currently disease-free. Small pilot studies have evaluated the impact of supplements, such as ginseng, vitamin D, and others, on CRF. However, there is no consistent evidence of their effectiveness.	Psychosocial interventions CBT/BT Mindfulness-based stress reduction Psychoeducational therapies/educational therapies Supportive expressive therapies Nutrition consultation CBT for sleep Stimulus control Sleep restriction Sleep hygiene **Pharmacologic interventions** Consider psychostimulants (methylphenidate) after ruling out other causes of CRF. Treat for pain, emotional distress, and anemia as indicated per NCCN guidelines Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities Repeat screening and evaluation	Exercise classes at cancer centers Community programs focused on cancer survivors Exercise professional certified by the American College of Sports Medicine For patients with CRF interfering with function, consider referral to a physical therapist or physiatrist **Other interventions** Psychosocial interventions Cognitive behavioral therapy/behavioral therapy Psychoeducational therapies/educational therapies Supportive expressive therapies Nutrition consultation Cognitive behavioral therapy for sleep Stimulus control Sleep restriction Sleep hygiene Acupuncture **Pharmacologic** Consider psychostimulants (methylphenidate) after ruling out other causes of CRF and failure of other interventions	All patients should be offered specific education about CRF prior to the start of treatment when CRF is identified and provided with strategies (e.g., physical activity, energy conservation, stress reduction and distraction) to manage CRF. To date, the use of pharmacologic agents to treat CRF is considered experimental (e.g., psychostimulants, sleep medications, low-dose corticosteroids such as prednisone or dexamethasone); therefore, it is not recommended except for selected patients at the end of life with severe CRF. Promote ongoing self-monitoring of CRF levels because CRF is still a common cancer-related side effect occurring in posttreatment survivors. For patients with advanced and progressive disease or are receiving active treatment, repeat ESAS screening and assessment as needed to determine any change in both subjective and objective aspects of CRF.

as the presence of concurrent symptoms such as anemia. Other potential treatable contributing factors including pain, emotional distress, sleep disruption, impaired functional status, medications, nutritional deficits, and comorbidities should also be assessed.

8.7 Treatment Options

All patients and/or their caregivers should be educated and counseled on the occurrence of CRF. Contributing factors that are identified should be treated accordingly. Non-pharmacological interventions such as exercise, psychosocial therapy, and mind-body approaches could be considered. The evidence for pharmacological interventions is limited and should be used judiciously.

8.8 Future Directions

As described above, much progress has been made in our understanding of CRF in the past decade. There is now a greater awareness and recognition that CRF is a major concern among cancer patients and survivors and that it is a multidimentional problem. The development of reliable and valid methods to measure CRF have facilitated better communication between healthcare teams and also allowed longitudinal monitoring of CRF. Knowledge in this area has also facilitated the selection of endpoints for clinical trials evaluating interventions targeting CRF. Published clinical trials in CRF have provided us a better understanding of the available options for managing CRF, specifically exercise, psychosocial therapy, and mind-body approaches. With increasing availability of well-conducted studies, multiple clinical practice guidelines have been created for the management of CRF. Lastly, we have an improved understanding of the biobehavioral mechanisms associated with the development of CRF.

Despite the progress, many research gaps exist in the area of CRF. The negative impact of CRF on other outcomes such as healthcare utilization, cost, and survivorship needs to be studied. Although studies have consistently demonstrated the benefits of exercise in CRF, the dose and intensity of exercise remain unclear. Given the multidimentional nature of CRF, a one-size-fits-all approach is likely not sufficient. Combinations of various strategies such as exercise and various psychological or biobehavioral interventions need to be further investigated. With an increasing emphasis of personalized medicine in oncology, it is crucial for us to understand the biobehavioral mechanisms associated with CRF in order to develop individualized interventions for patients and to know for whom and when specific treatments for CRF can be best prescribed. Finally, we need to disseminate the clinical practice guidelines into clinical settings in order to identify patients with CRF and implement these interventions for patients with cancer.

In conclusion, CRF is a common and debilitating toxicity for cancer patients and survivors and can persist for many years after treatment. Many instruments exist for measuring CRF and may be incorporated in the routine assessment of CRF. Exercise and psychological interventions have consistently demonstrated benefits in treating CRF and should be incorporated in the care of cancer patients and survivors.

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Distress

9

Linda E. Carlson, Kirsti Toivonen, and Peter Trask

9.1 Introduction

This chapter covers the topic of distress, known as the "sixth vital sign" in cancer care [1]. It can be a common misconception that surviving a cancer diagnosis and subsequent treatment means "problem solved" when in actuality one-third to one-half of survivors can experience distressing symptoms long after treatment has concluded [2–6]. Beyond the fact that distress can impair one's daily functioning and quality of life, there is evidence to suggest that high psychological distress may even relate to biological outcomes (e.g., inflammation, autonomic dysfunction, dysregulated hypothalamic-pituitary-adrenal axis activity), disease progression, and mortality [7, 8]. The increased focus on well-being in cancer care is timely in light of the imperative that cancer should be considered a biopsychosocial illness, not just a biomedical one [9], and treated more often as a chronic disease rather than an acute one.

This chapter also outlines definitions of distress, including depression and anxiety. Methods of screening for distress and the referral process are also discussed. The latter half of the chapter focuses on select evidence-based non-pharmacological interventions for treating distress in cancer survivors, specifically educational interventions, cognitive-behavioral interventions, problem-solving therapy (PST), and mindfulness-based interventions. This chapter does not represent a practical guide on how to conduct these interventions, nor is it a comprehensive literature review of every intervention available. Throughout this chapter, the term cancer survivor is consistently used to refer to anyone at any point in their cancer journey (e.g., from diagnosis to posttreatment). When referring to specific studies or policies, we will describe the sample of cancer survivors in that research (e.g., posttreatment cancer survivors, long-term cancer survivors, etc.).

This chapter represents the amalgamation of three separate chapters that were included in the first edition of the *Handbook of Cancer Survivorship*: *Depression*, by Trask & Pearman; *Psychological Distress, Depression, and Anxiety*, by Nezu & Nezu; and *Managing Daily and Long-Term Stress*, by Carlson & Speca. These three chapters were condensed, streamlined, and

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updated in order to reduce redundancy and improve convenience by grouping relevant information about psychological distress in one chapter. In the past decade, within each of these areas, many advances have been made; thus, the information provided in the chapter is as relevant, if not more so, than 10 years ago.

9.2 Distress

In this section we outline commonly accepted definitions of distress, anxiety, and depression, their prevalence among cancer survivors, common tools to assess them, and the referral process if these symptoms are detected. While many cancer survivors can report posttraumatic stress symptoms and have other psychiatric disorders following diagnoses, such symptoms are beyond the scope of this chapter (for a recent review of posttraumatic stress disorder and cancer, see Cordova et al. [10]).

Distress is generally defined as "a multifactorial 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" [11]. The word *distress* specifically is preferred as it can represent a wide array of emotional concerns and is not particularly stigmatizing [12]. 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" [11]. Although usually not as severe as a psychiatric diagnosis of anxiety or depression, the prevalence rates of distress are actually higher. An early study of 4496 individuals with a broad array of cancer types from the United States, representing varied time points in the disease trajectory (i.e., newly diagnosed to ≥4 years post-diagnosis), indicated that approximately 35% experienced distress [2]. Specifically, lung (43%), brain (43%), and Hodgkin's lymphoma (38%) survivors experienced the most distress, and gynecological cancer survivors (30%) experienced the least [2]. This is consistent with another early Canadian study that reported 38% of 3095 long-term cancer survivors (variety of cancer types, on average 3 years post-diagnosis) were significantly distressed according to Brief Symptom Inventory (BSI) criteria [3]. Cutoff scores for "significant distress" on the BSI and other instruments are usually determined by administering gold standard clinical interviews alongside screening tools to determine which score best discriminates people who are diagnosed with clinical anxiety or depression. People above the determined cutoff score are usually considered in need of professional support.

More recent studies using the distress thermometer (DT) have suggested similar distress prevalence rates. For example, studies of newly diagnosed individuals from Taiwan and China report 33% (using a cutoff score ≥4) and 22% (cutoff score ≥5) endorse clinically significant distress, respectively [4, 13]. An Italian study (in which nearly half of participants had been diagnosed with metastatic cancer) reported that 55% experienced clinically significant distress, and a Swedish study reported that 35% of those 6 months posttreatment experienced clinically significant distress [5, 6]. In sum, studies of distress prevalence suggest that distress is common among those with all types of cancer, across the entire disease trajectory, and across different countries; making it a global issue among cancer survivors.

Moreover, other concomitant symptoms among cancer survivors such as fatigue, insomnia, and pain can contribute to distress. For example, cancer-related fatigue is considered one of the most distressing side effects of cancer and treatment. Most studies report that 30–60% of survivors experience moderate to severe fatigue during treatment, and up to 30% of long-term survivors can continue to experience fatigue [14]. A meta-analysis of pain prevalence in over 30,000 cancer survivors indicates 39% experience pain posttreatment [15]. Finally, insomnia can occur more than twice as often in individuals who have been diagnosed with cancer than in the general population, and sleep disturbance is even more common [16]. Further, these symptoms can

coexist, precipitate, maintain, or exacerbate one another. For example, a study of cancer survivors (two-thirds of participants were posttreatment) in the United Kingdom showed those with sleep problems (865/2862 or 30.2%) were more likely to report pain and emotional distress [17].

A longitudinal study of individuals newly diagnosed with cancer reported that symptoms tended to cluster together. Clusters of somatic symptoms (including pain, fatigue, and sleep), psychological symptoms (including anxiety and depression), and nutrition-related symptoms (including weight loss/gain and altered food intake) were observed, with greater symptom burden relating to higher overall distress [18]. Taken together, the evidence suggests that adverse side effects of cancer and its treatment seldom occur in isolation and can create considerable symptom burden for survivors.

These findings highlight the need to address continuing symptoms of distress among cancer survivors as they move forward in their recovery. In recognition of the importance of this issue, distress screening has been endorsed by accreditation organizations including the World Health Organization and the International Psycho-Oncology Society and in journals such as the Journal of Clinical Oncology [1] and Psycho-Oncology [9]. It has also been recommended that distress be treated as a critical element in cancer care and assessed at every follow-up visit [19], just as one would assess the other vital signs. The American College of Surgeons has mandated the routine screening of distress for all cancer patients as an accreditation requirement beginning in 2015 [20]. This same mandate has been in effect in Canada since 2009 [21], spearheaded by the Canadian Partnership Against Cancer [22].

9.3 Screening for Distress

Methods and models for efficient distress screening have been published [23, 24]. Guidelines for screening have also become available. The National Comprehensive Cancer Network (NCCN) guidelines recommend assessing and managing distress, including (but not limited to): recognizing, monitoring, documenting, and promptly treating distress; screening distress at the initial visit, at intervals during treatment and follow-up, when clinically indicated, and at status changes such as remission, recurrence, or progression; identifying the level and nature of the distress; and assessing and managing distress in accordance with clinical practice guidelines [11] (the full Distress Management guidelines are available at the NCCN website:https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#distress).

The Canadian Association of Psychological Oncology's (CAPO) Pan-Canadian Practice Guideline is consistent with NCCN guidelines and includes further recommendations to screen specifically for global anxiety symptoms and generalized anxiety disorder in addition to general distress [24]. The CAPO guidelines can be accessed online at https://www.capo.ca/wp-content/uploads/2015/11/FINAL_Distress_Guideline1.pdf. Recommendations for distress screening from the joint task force of the American Psychosocial Oncology Society, the Association of Oncology Social Work, the Oncology Nursing Society [25], and from the American College of Surgeons Commission on Cancer [20] are also consistent with NCCN and CAPO guidelines. Although distress screening is necessary, it is not sufficient to address psychosocial issues in cancer care – distress symptoms must be adequately followed up, triaged, and referred for appropriate treatment [26]. The referral process is elaborated later in this chapter.

9.3.1 Tools for Distress Screening

Several brief tools are available for distress screening. While some more broadly focus on general distress, others ask about specific symptoms such as depression and anxiety. The most often used distress screening tools based on a systematic review of randomized controlled trials of psychological interventions for cancer survivors were the distress thermometer (DT), the Hospital Anxiety and Depression Scale, and the

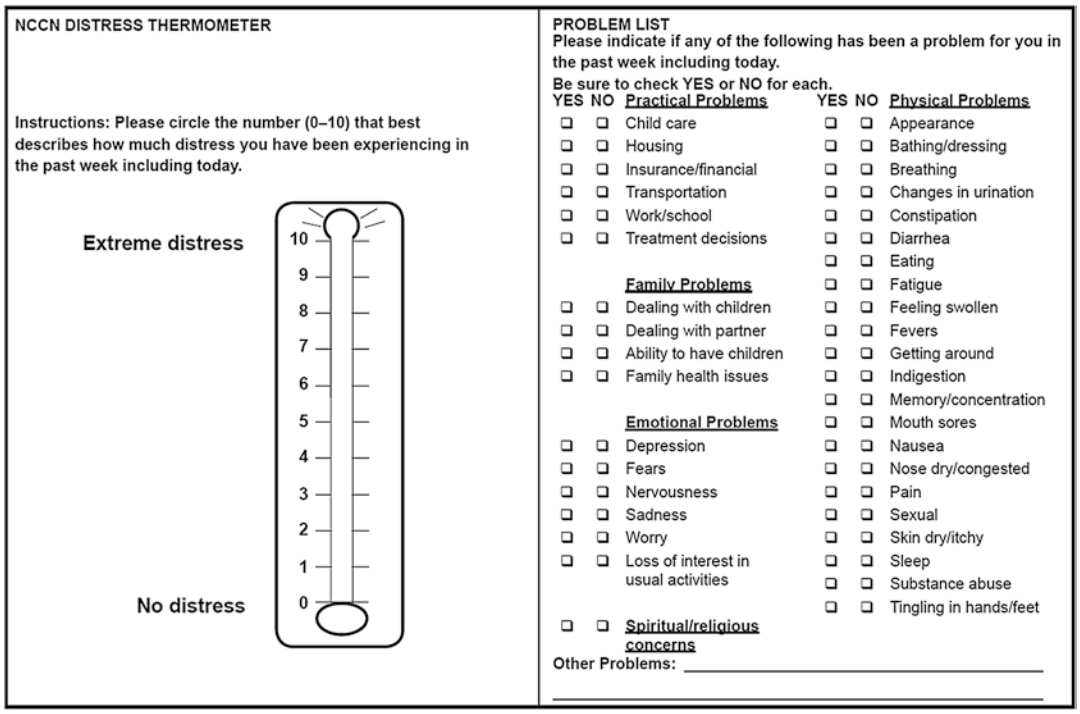

Fig. 9.1 The NCCN distress thermometer and problem list [11])

Profile of Mood States-short form [27]. A more comprehensive list of tools is available [23]. We will also describe the Brief Symptom Inventory and the Edmonton Symptom Assessment System-revised, both included in large-scale studies of distress in survivors [2, 3] and as recommended assessment tools for distress screening [24].

The DT is a single-item measure of global distress that asks individuals to rate, on a scale of 0 (*no distress*) to 10 (*extreme distress*), how much distress they have been feeling in the past week, including the present day [11]. The DT can be completed orally or presented visually as an image of a thermometer. It is often accompanied by a problem list where individuals can indicate which areas they are specifically having difficulty (see Fig. 9.1).

A review of 57 studies worldwide using the DT for screening distress in cancer survivors (compared to other symptom inventories and diagnostic interviews) reported that the cutoff score of four maximized sensitivity and specificity in the majority of studies [28], thus a threshold of four or greater is most widely considered to indicate clinically significant distress. The brevity of the distress thermometer is ideally suited to minimizing survivor burden while maximizing uptake in clinical practice. Further, it is versatile, having been validated for use in people with several different cancer types [29] and in many different languages [28].

The Hospital Anxiety and Depression Scale (HADS) is a 14-item checklist often used for distress screening, though it actually measures symptoms of anxiety and depression. For each item, the patient ranks depression and anxiety symptoms on a scale of 0 (absence of a symptom) to 3 (strong presence), yielding separate scores for each group or a total general distress score [30]. The HADS purposefully excludes physical symptoms of anxiety and depression, which often overlap with the physical symptoms reported by chronic illness populations, to prevent inflation of depression and anxiety scores due to symptom overlap. The HADS (the depression subscale in particular) has shown good diagnostic accuracy in populations of cancer survivors [31] and has been frequently used, often as the "gold standard"

comparator in studies of newer screening instruments. For example, nearly every validation study of the DT reported by Donovan et al. [28] compared the DT to the HADS.

The Profile of Mood States (POMS)-short form is a 37-item measure of different moods (e.g., tense, angry, worn out) ranked from 0 (*not at all*) to 4 (*extremely*) that can provide mood disturbance scores in different domains (i.e., tension-anxiety, depression, anger-hostility, vigor-activity, fatigue, and confusion-bewilderment) as well as a total mood disturbance score [32]. The POMS has been shown to be psychometrically sound in populations of cancer survivors [33]. However, it is more often used as an outcome measure in clinical intervention studies than as a screening tool, due primarily to its length.

The Brief Symptom Inventory-18 is an abbreviated version of the Symptom Checklist-90, a classic measure of distress, that assesses 18 distress-related items on a scale of 0 (*not at all*) to 4 (*extremely*) over the past 7 days [34]. It provides scores for somatization, depression, and anxiety as well as providing a global severity score, has normative data for newly diagnosed cancer survivors specifically [35], and has been used to screen distress in thousands of cancer survivors as part of large studies in Canada [3] and the United States [2].

The Edmonton Symptom Assessment System-revised version is a 10-item tool that assesses on a scale of 0 (*none*) to 10 (*worst possible*) how one is *now* experiencing a variety of symptoms (e.g., pain, tiredness, lack of appetite) and has a tailored question at the end to apply to a particular symptom not mentioned that a survivor may be experiencing [36]. It was initially developed for individuals with advanced cancer [36] but has been used in many large-scale screening programs in multiple populations with chronic illness, particularly in Canada [37, 38].

9.3.2 Tools for Needs Assessment

If distress is identified in a cancer survivor, an assessment of specific needs is important for identifying the nature of the concerns and specific areas to target to aid in the referral process. The distress thermometer is often accompanied by a short problem list that similarly asks survivors to indicate from a list of practical (e.g., child care, finances), family (dealing with a partner), emotional (e.g., depression), physical (e.g., getting around), or spiritual (lack of meaning in life) problems (see Fig. 9.1). The checklist asks whether any have been a problem for them in the past week, including the present day [11].

A 2012 review by Carlson et al. [23] examined distress screening and needs assessment tools and recommended the following tools as having undergone the most rigorous psychometric testing: the Cancer Care Monitor, Cancer Rehabilitation Evaluation System and short form, Cancer Needs Distress Inventory, Supportive Care Needs Survey and short form, and Cancer Survivors Unmet Needs. These measures are longer (34–139 items) than distress screening tools and assess practical domains such as physical symptoms, medication side effects, sexual/marital functioning, or healthcare needs [23].

9.4 Anxiety

Careful distinction should be made between symptoms of anxiety and a diagnosed anxiety disorder. Anxiety symptoms are those typically measured with self-report scales in this context and can include worry, restlessness, poor sleep, and somatic symptoms. A diagnosed anxiety disorder is verified by a psychologist, psychiatrist, or physician according to specific diagnostic criteria following a structured clinical interview and indicates clinically significant impairment in functioning. Anxiety symptoms can contribute to the broad concept of distress; however, anxiety is distinct in that it specifically refers to apprehension about future events or outcomes while distress can be related to future, present, or past factors.

Anxiety is common among cancer survivors. For example, a meta-analysis of 3623 ovarian cancer survivors reported that 19% had anxiety (indicated by scores exceeding a critical cutoff

measure on self-reported anxiety questionnaires such as the HADS) pretreatment, 26% had anxiety during treatment, and 27% had anxiety post-treatment [39]. Accordingly, a meta-analysis of 4494 prostate cancer survivors reported 27%, 15%, and 18% of respondents had anxiety before, during, and after treatment, respectively [40]. Several reasons, including fear surrounding diagnosis, fear of treatment side effects or future disease progression or recurrence, fear of death and of the unknown, and actual side effects or disease progression, are factors that may underlie why cancer survivors can experience anxiety.

9.4.1 Measures Used for Assessing Anxiety

Paralleling the distinction between symptoms of anxiety and diagnosed anxiety disorders, there are tools for measuring anxiety symptoms and diagnostic instruments. Some examples of anxiety symptom instruments are the State-Trait Anxiety Inventory (STAI) and the Beck Anxiety Inventory (BAI). The STAI is a 40-item measure of anxiety experienced in the moment (e.g., "I am tense") and anxiety experienced generally (e.g., "I am a steady person") on a 4-point scale. A systematic review of anxiety in breast cancer reported the STAI as one of the most frequently used scales to measure anxious symptoms [41]. The BAI is a 21-item self-report measure of cognitive, somatic, and emotional symptoms of anxiety rated on a 4-point scale of 0 (*not at all*) to 3 (*severely*). It has been validated for use in multiple languages with cancer survivor populations [42]. The benefits of using symptom inventories include the brief time involved in completing and administering the questionnaire (thus easing burden on survivors and health-care providers) as well as the low cost for tool administration. Information about the severity of symptoms can be gleaned, thus making these inventories ideal for progress monitoring. While the potential lack of detail about possibly relevant areas and lack of opportunity to ask follow-up questions are limitations of self-reported anxiety measures, their primary drawback is that their use cannot result in diagnosis.

For situations where a diagnosis is required, there are three major diagnostic instruments; the Schedule for Affective Disorders and Schizophrenia (SADS) [43], the Structured Clinical Interview for the DSM-5 (SCID) [44], and the Diagnostic Interview Schedule (DIS) [45]. Such instruments are lengthy, semi-structured, or structured interviews that align questions with diagnostic criteria in the DSM [46]. The obvious appeal of diagnostic interviews is their ability to result in diagnosis of an anxiety disorder; they are considered the gold standard for diagnosing any mental disorder. Further, (semi-structured) interviews can allow for more flexibility to follow up in specific areas of interest. Drawbacks of using such instruments include the time and cost required.

9.5 Depression

Depression refers to persistent low mood or loss of interest or pleasure in activities and can be accompanied by fatigue, guilt/worthlessness, and changes in activity level, sleep, or weight [46]. While depression can contribute to broad, overall distress (hence why the HADS is considered a scale of psychological distress), it represents its own distinct construct. As with anxiety, a distinction must be made between depressive symptoms and a diagnosis of major depressive disorder. Depressive symptoms are also common among cancer survivors. For example, Watts et al.'s meta-analysis of depressive symptoms (measured with self-report scales) in 3623 ovarian cancer survivors reported 25% experienced symptoms before, 23% during, and 13% after treatment (2015) [39]. Their meta-analysis of 4494 prostate cancer survivors reported 17%, 15%, and 18% experienced depressive symptoms before, during, and after treatment, respectively (2014) [40].

Cancer survivors are more likely to experience depressive symptoms than the general population. Risk factors such as family history of depression, individual history of depression, being female, poor social support, earlier age of illness onset, longer length of illness, and

biological variables (e.g., gene-stress susceptibility, altered stress response, and inflammation) can make survivors more vulnerable to experiencing depressive symptoms [47]. Further, there are reports that certain anticancer pharmaceuticals such as corticosteroids, chemotherapy agents (e.g., alkylating agents), and hormones have resulted in "depressogenic effects," though the evidence is equivocal [48]. It should be noted that most prevalence studies of "anxiety" and "depression" are conducted with self-report questionnaires rather than structured clinical interviews leading to confirmed diagnoses. Thus, prevalence estimates may not be representative of actual rates of diagnosis.

9.5.1 Measures Used for Assessing Depression

As with tools for assessing anxiety, there are depressive symptom inventories (meant solely to describe specific symptoms) that are separate from diagnostic instruments (used to determine whether symptoms are severe and frequently occurring enough to warrant a psychiatric diagnosis). Common tools for measuring depressive symptoms include the following self-report measures: the Beck Depression Inventory-II (BDI-II), the Centre for Epidemiologic Studies Depression Scale (CES-D), the Patient Health Questionnaire-9 (PHQ-9), and the Zung Self-Rating Depression Scale (Zung SDS). The BDI-II is a 21-item scale of various symptoms (e.g., cognitive, affective, physical) related to depression on a 4-point scale that one has been experiencing in the past 2 weeks [49]. The CES-D has 20 items on a 4-point scale about symptoms experienced in the past week that are associated with a clinical diagnosis of depression [50]. A recent review of self-reported depression measures used in clinical oncology reported that the BDI-II was relatively more generalizable across different cancer types with good "case-finding" ability, and the CES-D was the best measure for responsiveness to change [51].

The Zung SDS is a 20-item measure that assesses the extent to which one endorses a series of positive and negative statements "during the past several days" on a 4-point scale [52]. The PHQ-9 is a 9-item measure that assesses presence of depressive symptoms over the past 2 weeks and includes an additional item assessing the extent of impairment resulting from the symptoms [53]. It is often used in medical settings as a screening tool for major depression. Gold standard instruments such as the SADS, the SCID-5, and the DIS follow diagnostic criteria and can provide a diagnosis of depression. The benefits and drawbacks of symptom inventories and diagnostic interviews discussed regarding anxiety (see section above) are also pertinent to depression. Table 9.1 provides an overview of measures used for assessing distress, anxiety, and depression.

9.6 Diagnostic Considerations

One important issue to consider is that clinical interviews were developed and validated on populations that did not have major comorbid medical illnesses; thus, the criteria may not be completely generalizable to illness populations. For example, diagnosing depression in cancer survivors can be difficult due to the similarity between depressive symptoms and symptoms of cancer or its treatment. For example, cancer treatments such as chemotherapy or radiotherapy often result in fatigue, weight loss, anhedonia, cognitive changes, or psychomotor retardation. Thus, it can be difficult to delineate the origins of the observed symptoms. While this symptom overlap can contribute to overdiagnoses of depression, it may also mask potential depressive symptoms and contribute to missed diagnoses in certain cases.

In an attempt to identify an accurate method of assessing depression in cancer survivors, researchers have employed several approaches: inclusive (i.e., considering all symptoms regardless of whether they are secondary to a physical illness), etiologic (i.e., only considering symptoms not clearly resulting from physical illness), substitutive (i.e., replacing symptoms that may

Table 9.1 Overview of tools for evaluation of distress, anxiety, and depression

Tool	Purpose	Description
Beck Anxiety Inventory (BAI)	Measures severity of anxiety symptoms	• Self-report • 21 items, scale of 0–3
Beck Depression Inventory-II (BDI-II)	Measures severity of depressive symptoms in the past 2 weeks	• Self-report • 21 items, scale of 0–3
Brief Symptom Inventory (BSI)	Measures severity of distress symptoms, including somatic, depressive, and anxious symptoms	• Self-report • 18 items, scale of 0–4 • Yields scores for somatization, depression, anxiety, and global severity
Centre for Epidemiologic Studies Depression Scale (CES-D)	Measures severity of depressive symptoms in the past week	• Self-report • 20 items, 4-point scale
Diagnostic Interview Schedule (DIS)	Diagnostic interview; used to determine if symptoms of anxiety or depression meet criteria for a diagnosis of a psychological disorder	• Number of questions and length of interview varies depending on the number of symptoms experienced • Must be administered
Distress thermometer (DT) and problem list	Measures distress severity in the past week, as well as different areas where problems may be experienced	• One item, scale of 0–10 • Problem list assesses practical, family, emotional, spiritual, and physical concerns
Edmonton Symptom Assessment System-revised (ESAS-r)	Measures severity of psychological (e.g., anxiety) and physical (e.g., pain) symptoms	• Self-report • 10 items, scale of 0–10 • Includes a diagram of the body where pain can be indicated
Hospital Anxiety and Depression Scale (HADS)	Measures severity of symptoms of distress and anxiety independent of overlapping symptoms common among those with medical illness	• Self-report • 14 items, scale of 0–3 • Yields separate scores for anxious symptoms and depressive symptoms as well as general distress score
Patient Health Questionnaire-9 (PHQ-9)	Measures severity of depressive symptoms over the past 2 weeks	• Self-report • 9 items, scale of 0–3
Profile of Mood States-short form (POMS-37)	Measures severity of mood disturbance, including domains of tension, depression, anger, vigor, fatigue, and confusion	• Self-report • 37-items, scale of 0–4 • Yields scores for each domain as well as total mood disturbance
Schedule for Affective Disorders and Schizophrenia (SADS)	Diagnostic interview; used to determine if symptoms of anxiety or depression meet criteria for a diagnosis of a psychological disorder	• Number of questions and length of interview varies depending on the number of symptoms experienced • Must be administered
State-Trait Anxiety Inventory (STAI)	Measures severity of anxious symptoms at present and in general	• Self-report • 40 items, 4-point scale
Structured Clinical Interview for the DSM-5 (SCID)	Diagnostic interview; used to determine if symptoms of anxiety or depression meet criteria for a diagnosis of a psychological disorder	• Number of questions and length of interview varies depending on the number of symptoms experienced • Must be administered
Zung Self-Rating Depression Scale (Zung SDS)	Measures severity of depressive symptoms	• Self-report • 20 items, 4-point scale

be related to a physical illness with additional cognitive symptoms), and exclusive (i.e., eliminating fatigue and appetite/weight changes from consideration) [54]. Consequently, prevalence of depression can vary among the same group of individuals depending on which approach is used to determine diagnoses. Consider the following example:

> Curtis is a 56-year old man who has been undergoing chemotherapy. He has been experiencing low mood and a loss of interest in activities he usually enjoys for the last month. In addition, he reports

sleep difficulties, extreme fatigue, and no appetite nearly every day. Given that fatigue and loss of appetite are common side effects of chemotherapy, it is difficult to discern whether these symptoms are due to his treatment or due to depression. A clinician following an inclusive approach would consider all these symptoms, regardless of their cause, and could diagnose Curtis with Major Depressive Disorder. A clinician following an exclusive approach would not want to consider fatigue and change in appetite when making a diagnosis since they may not be due to depression, and thus would not provide a diagnosis of Major Depression, but rather Adjustment Disorder.

Another pertinent issue is age of the survivor. Symptoms due to aging can overlap with depressive symptoms, which may result in missed diagnoses of depression in the elderly. For example, changes in sleep, appetite, energy, and mood may be perceived as general changes that occur with aging (e.g., physical changes, loss of social support, medications), rather than due to a depressive disorder. Further, the most commonly used measures of depressive symptoms have not been tested or validated in geriatric cancer survivor populations and may miss symptoms of depression unique in this population [55]. NCCN guidelines for geriatric cancer survivors recommend the Geriatric Depression Scale (GDS) for screening for depression among older cancer survivors, particularly when cancer-related fatigue is reported as they often co-occur [56]. However, a 2016 study reported that recommended cutoff scores for three popular measures of depression (GDS-short form, HADS, CES-D) were not adequately sensitive to detect depression among senior cancer survivors, suggesting that lower cutoff scores should be considered for this population [57]. To illustrate diagnostic considerations with geriatric samples, consider the following:

Doreen is a 73-year-old woman who had completed treatment for breast cancer years earlier without any signs of recurrence. Over the past few months, she has expressed feeling "very down" most of the day, almost every day. She also reports fatigue, low appetite, and sleep difficulties, especially early morning awakenings. She also experiences aches and pains, which she reports "slow her down" in doing everyday activities. It is difficult to determine whether her fatigue, sleep difficulties, and appetite symptoms are symptoms of depression, or due to changes that occur with age. She might be administered the Geriatric Depression Scale rather than a Beck Depression Inventory (or CES-D) as a diagnostic tool, which omits questions regarding sleep and appetite, and has a greater focus on cognitive symptoms (e.g., hopelessness, feelings of worthlessness, memory problems).

9.7 The Referral Process

Once distress, anxiety, and/or depression are identified, referrals should be made to direct cancer survivors to appropriate resources and support to improve their well-being. Distress screening recommendations from the American Psycho-Oncology Society, Association of Oncology Social Work, and Oncology Nursing Society Joint Task Force acknowledge that distress screening should only be implemented after a plan for referral and management exists, as distress screening is only positively related to patient outcomes when treatment is received [25, 58, 59]. They recommend developing a standardized protocol for reviewing results of screening, determining when follow-up assessment is necessary, and referring to resources in a timely manner. They also recommend, if possible, having a clinician or team of clinicians (e.g., nurses, social workers, psychologists, physicians) involved in the screening and referral process. In addition, Carlson [26] notes the importance of staff education and training in the successful implementation of a distress screening and referral program.

An important element of distress screening is the appropriate triage of symptoms to most effectively provide referrals and services. A stepped-care model is recommended, wherein all individuals receive education and information (normalcy of distress in cancer, peer support groups, practical resources, specific stress reduction strategies, self-management strategies to manage other symptoms, and non-pharmacological strategies) and further resources graded to symptom severity. The Pan-Canadian Guidelines provide an algorithm to aid in decision-making regarding referrals (see Fig. 9.2). According to the algorithm, initial screens should occur upon entry to the system and at critical times in the disease or treatment process, points of

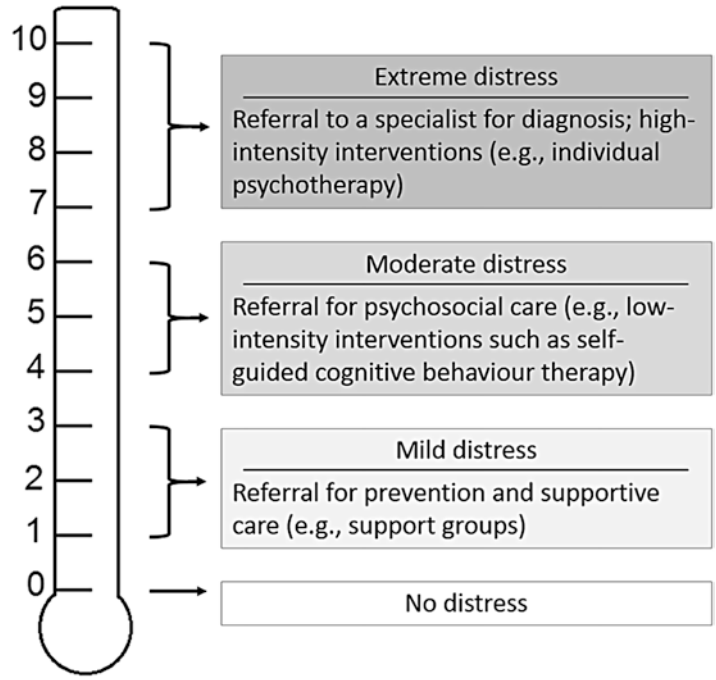

Fig. 9.2 Distress thermometer (DT) [11] with cutoff scores for triaging of referrals [24]. The DT asks individuals to rate, on a scale of 0 (*no distress*) to 10 (*extreme distress*), how much distress they have been feeling in the past week, including the present day [11]. Cutoff scores for distress severity are based on the Pan-Canadian Practice Guidelines [24]

transition, or during stressful life-course events. If there is immediate risk of harm to self or others, the individual should be referred to urgent care. Otherwise they should be assessed with standardized, validated distress screening measures.

Those who endorse *mild* distress, anxious, or depressive symptoms (e.g., 1–3 on the DT) would be considered to have normal worries in response to the situation and will likely experience gradual reduction of symptoms over time. For example, one study of breast cancer survivors reported that most experience a reduction in distress, depressive, and anxiety symptoms by approximately 4 months following diagnosis [60]. Those with mild distress would be offered information for self-referral to psychosocial support/peer support groups and general psychoeducational materials [24]. Given that mild distress would lead to a referral for low-intensity interventions like support groups, it is possible that natural remission of distress may contribute to their effectiveness. A review of cancer support groups suggests that support groups are associated with participant satisfaction and improvements in quality of life [61]. The evidence for psychoeducational interventions is discussed in Sect. 9.8.1.

Anyone who endorsed *moderate* (e.g., 4–6 on the DT) or *severe* (e.g., 7–10 on the DT) distress, anxiety, or depression would be given a more comprehensive assessment to discern the nature and extent of the distress (e.g., interference in daily functioning, the most distressing symptoms, other risk factors) and would be assessed for more specific depressive symptomology. Those with moderate distress, depressive symptoms or anxiety symptoms plus impairment in functioning (e.g., difficulties at work, maintaining a home, or in relationships) would be referred to psychological services as required. Moderate distress may warrant referral to low-intensity group or brief (3–5 visits) individual interventions such as behavioral activation, mindfulness-based stress reduction, problem-solving therapy, guided self-help, and possible pharmacotherapy [24].

Those with *severe* distress, depressive symptoms, or anxious symptoms would receive a referral to a specialist for diagnosis and likely receive

high-intensity interventions (e.g., cognitive behavior therapy, interpersonal therapy, pharmacotherapy), and those at immediate risk of harming themselves or others would receive urgent care [24]. All individuals would receive follow-up and ongoing reassessment as necessary.

Considerations for providing referrals include the context of patient-health-care provider interaction and individual wishes. A recent study of survivors calling a cancer helpline indicated that while most of the individuals calling the helpline had DT scores suggesting they would require follow-up care, only 16% were offered referrals from nurses [62]. It may be that survivors are more likely to get referrals following face-to-face interactions. Interestingly, a recent survey of 1340 cancer survivors regarding referral wishes reported that 13% wished for a referral and a further 21% would consider a referral to psychological or paramedical services [63]. Those who wished to have a referral were more distressed, younger, more likely not to have children, more educated, more likely to be employed, recently diagnosed/in active treatment, receiving more intensive treatment, and more likely to perceive support they had already received as insufficient [63]. Another study that examined self-referral patterns in over 500 people newly diagnosed with cancer reported that over a 12-month period, only 24% accessed services related to distress management [64]. Although those in this study who endorsed higher levels of distress were more likely to access services, most (71%) of those who endorsed high distress at least once over the course of the study still did not access services.

Results of these studies suggest that some individuals may be hesitant to take a referral despite experiencing significant distress. Potential reasons for lack of referral despite distress may include 1) lack of belief that psychosocial services will be effective, 2) lack of time/energy to visit another health-care provider in addition to visits for primary cancer treatment, 3) potential embarrassment or stigma around seeking psychological services, or 4) lack of financial resources when survivors may need to pay for services out of pocket. Psychoeducation about the prevalence of distress in cancer survivors aimed at normalizing distress, information about the effectiveness of different psychological resources, and provision of free or low-cost resources for managing distress may help mitigate these barriers. *Cancer.Net* provides psychoeducational information, tips for managing mild distress, and resources for additional support (e.g., helplines, online support groups, tips for finding a local counselor) at http://www.cancer.net/coping-with-cancer.

While the focus of this chapter is on general distress, other problems and symptoms identified in the screening process such as pain, fatigue, insomnia, nausea, and practical concerns such as finances or drug coverage would receive referrals to appropriate staff as available (such as pain clinics or social work) or be managed by the oncology care team on a case-by-case basis.

9.8 Evidence-Based Psychosocial Interventions for Cancer Patients

Thus far we have considered evaluation of distress and referral to appropriate sources, when distress is identified. The remainder of the chapter is dedicated to describing select interventions for distress management in cancer survivors and research regarding outcomes. Educational interventions, cognitive-behavioral interventions, problem-solving therapy, and mindfulness-based interventions will be discussed. For an overview of the interventions discussed, their rationales, and a summary of supporting evidence, see Table 9.2.

9.8.1 Educational Interventions

The major goals of educational interventions are to reduce feelings of distress and improve the sense of control that may be threatened by lack of knowledge or feelings of uncertainty. Specific topics may include the technical aspects of cancer and its treatment, potential

Table 9.2 Interventions, theoretical rationale, and evidence for outcomes

Intervention	Purpose	Evidence
Cognitive-behavior therapy (CBT)	• Targets interrelated maladaptive thoughts, negative feelings, and behaviors through techniques such as cognitive restructuring, behavioral activation, and exposure	• Improvements in depression, anxiety, quality of life, and vigor; not pain or physical functioning [65–69] • Also appears effective when targeted for specific symptoms such as insomnia [70]
Educational/ psychoeducational interventions	• Improves knowledge about treatment, side effects, and the medical system to reduce feelings of uncertainty • Improves knowledge about psychological problems and treatment to normalize feelings and promote treatment buy-in/adherence	• Educational interventions result in improvements in knowledge [71] • Education is not sufficient to improve symptoms of depression, anxiety, pain, physical functioning, or quality of life [65, 66, 72] • Psychoeducational may help improve psychological outcomes in the short term [73]
Mindfulness-based stress reduction (MBSR)	• Aims to improve moment-to-moment nonjudgmental awareness and attitudes of openness and acceptance, primarily through meditation • Focus on present awareness specifically helpful for uncertainties surrounding cancer (e.g., outcomes, recurrence)	• Evidenced to improve mindfulness, mood disturbance, distress, anxiety, depression, fear of cancer recurrence, and biological outcomes (e.g., cortisol, inflammatory markers, telomeres) [74–82]
Problem-solving therapy (PST)	• Targets problem navigation and problem-solving skills to improve coping strategies and perceived control over stressful situations • Meant to be helpful when distress is based on realistic concerns rather than cognitive distortions	• Appears to help survivors manage uncertainty, improve coping skills, and improve mood/ psychological outcomes [83–85] • May be particularly beneficial when caregivers are also provided with PST [86]

side effects (e.g., prevalence, course), navigating the medical system, and the physician-patient relationship. Psychoeducation, distinct from general education by providing information specific to mental health and psychological problems (e.g., prevalence of problems, precipitating factors, maintenance factors, and treatment), is also important. Possible benefits of psychoeducation include normalizing cancer-related distress, depression, and anxiety; informing individuals about treatment options to facilitate preference-based treatment; and informing individuals about the efficacy of psychosocial interventions, thus promoting treatment buy-in and adherence.

Early reviews of educational interventions for cancer survivors report positive effects on outcomes such as knowledge, symptom management, and health-care utilization, but no effect on distress, mood, depression, anxiety, pain, physical functioning, or quality of life [65, 71]. A more recent 2009 meta-analysis of 21 trials of educational interventions specifically targeting cancer pain reported significant improvements in pain, mixed results regarding self-efficacy to manage pain, and no benefit for pain interference [72].

A 2011 review of randomized controlled trials (RCTs) of psychosocial interventions for cancer survivors included six studies of psychoeducational interventions, concluding that the interventions did not improve quality of life or mood, but improved fatigue in the short term [66]. A 2013 meta-analysis of RCTs of psycho-oncologic interventions for cancer survivors included 19 studies of psychoeducation [73]. Results included small effect size improvements for emotional distress, anxiety, depression, and quality of life in the short term; but only improvements in quality of life were maintained in the long term. This meta-analysis also included 23 interventions consisting of "information only," but described no significant improvements from these interventions.

It is not surprising that educational interventions would result in increased knowledge and

health-care utilization. However, it appears that educational interventions are not effective for improving specific outcomes related to depression, anxiety, physical functioning, or quality of life; and results are mixed for pain. Thus, while providing education to individuals is likely necessary for their care, it is not sufficient for improving psychological outcomes. Psychoeducational interventions, in contrast to education alone, appear to be more effective for improving psychological outcomes, likely due to the focus on these outcomes as targets of psychoeducational interventions.

9.8.2 Cognitive-Behavioral Interventions

Cognitive behavior therapy (CBT) is based on an empirical foundation focused on the interrelationships among behaviors, thoughts, emotions, and biological events. CBT interventions operate under the principles that 1) thoughts can be accessed, 2) thoughts mediate emotional and behavioral responses, and 3) responses to events can be modified [87]. 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 of the strategies under the CBT umbrella are more behavioral in nature, theoretically based on principles of respondent and operant conditioning. Such strategies include contingency management (e.g., changing the consequences of behavior to change the behavior) and systematic desensitization. Other strategies are focused on altering cognitions and include techniques such as cognitive restructuring and cognitive distraction.

CBT can be applied to help cancer patients with overall distress and quality of life, as well as specific negative symptoms (e.g., anticipatory nausea, pain). For example, a meta-analysis of CBT tailored for treating insomnia symptoms has been shown to improve multiple indices of sleep (sleep efficiency, sleep latency, waking after sleep, and self-reported insomnia severity) in cancer survivors [70]. A systematic review and meta-analysis of 11 studies of CBT (defined by the authors as any approach that assumes cognitions can be altered and monitored) for cancer survivors reports large effect size improvements in depression, anxiety, and quality of life, but no differences in pain or physical functioning relative to control [65]. Improvements in mood disturbance, depression, and vigor following CBT for breast cancer survivors specifically are also supported by a review, though the specific content of the CBT interventions was not always described [67].

More recent systematic reviews have described the effectiveness of CBT for breast cancer survivors. Fors et al. report preliminary evidence for the effectiveness of CBT for improving quality of life [66]; Xiao et al. report that CBT effectively reduces depressive symptoms [68]; and Jassim et al. concluded that CBT is beneficial for reducing anxiety, depression, and mood disturbance, but not for improving survival [69]. The specific interventions described by these studies included behavior modification/reinforcement, relaxation training [68, 69], cognitive therapy [68], coping skills training, systematic desensitization, biofeedback [69], stress management, or "general CBT" [66].

A recent meta-analysis examined CBT (including components such as social skills training, problem-solving, cognitive restructuring, and relaxation training) for improving psychological outcomes in the caregivers of cancer survivors [88]. While small effect size improvements in multiple facets of well-being were reported, they were not maintained when analyses were restricted to RCTs only. The authors speculated that the ineffectiveness of CBT for caregivers may be explained by floor effects (i.e., caregivers were not distressed enough for significant improvement to occur), the content of thoughts being realistic (i.e., distress was due to realistic concerns rather than distorted cognitions), or variability in the purity of the interventions used.

Cognitive behavioral stress management (CBSM) is a specific CBT-based intervention developed by the Miami Behavioral Medicine group in the 1980s that has been extensively

applied to cancer survivors. The 10-week manualized, structured group program covers a variety of areas (e.g., stress awareness, identification of automatic thoughts and cognitive distortions, physical relaxation, meditation, and social support) and has been reformulated for cancer populations specifically [89]. In breast cancer survivors, CBSM has resulted in improved cognitive and affective outcomes [90], improved sleep quality and decreased fatigue [91], decreased cortisol [92], improved immune response [93], and attenuated expression of genes representing pro-inflammatory, antiviral, and antibody production signaling [94]. Further, the effects of CBSM appear to be long-lasting: follow-up results of breast cancer survivors who had received CBSM continued to report significantly lower rates of depression after 5 [95] or even 11 [96] years. In prostate cancer survivors, CBSM has similarly resulted in improved physical well-being, emotional well-being, total well-being, and sexual functioning [97].

Overall, CBT interventions generally seem to be effective for improving multiple psychological outcomes among cancer survivors, particularly those who have been diagnosed with breast cancer. However, given the great variability in interventions that are included under the CBT umbrella, future reviews should examine whether the effectiveness of CBT interventions differs depending on the specific intervention types (e.g., comparing predominantly behavioral interventions to predominantly cognitive ones). Additionally, while breast cancer survivors have been well-studied, further reviews should also examine the effectiveness of CBT for other cancer types.

9.8.3 Problem-Solving Therapy

Problem-solving in real-life situations is considered an important psychological variable that mediates the impact of cancer [98]. As a therapy, it promotes general coping ability that enhances adaptability, feelings of flexibility, and perceived control in stressful situations [99]. 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 daily problems and problem-solving as a means of coping with them. 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. Revised guidelines have been published describing PST for cancer patients that summarize specific tools [100].

The effectiveness of PST has been demonstrated across a range of patient populations, different age groups, and various types of psychological difficulty [101]. Positive effects of PST for cancer survivors include managing uncertainty [83], improved coping, improved mood, decreased marital and sexual difficulties [84], and reduced symptom limitations [102]. Mothers of children with newly diagnosed cancer who received PST have developed enhanced problem-solving skills and decreased negative affect [103], though the long-term effects may not be as strong as those observed posttreatment [104]. PST has also resulted in significant improvements in depression, environmental reward, anxiety, quality of life, social support, and medical outcomes among breast cancer survivors also diagnosed with major depression [85]. Further, high patient satisfaction with the protocol was reported, and treatment gains were maintained at a 12-month follow-up.

There is evidence to support the effectiveness of integrating caregivers in PST. Nezu and colleagues conducted a RCT comparing individual PST, PST provided to survivors and their caregivers, and treatment as usual for improving quality of life in distressed cancer survivors [86].

Both treatment conditions were found to result in decreased distress and improved quality of life across self, significant other, and clinician ratings immediately post-intervention; however, at a 6-month follow-up, those who received PST alongside a caregiver continued to improve more than those who received individual PST. Further, improvements in problem-solving were correlated with decreases in psychological distress and improvements in overall quality of life. In addition to integrating caregivers into PST for cancer survivors, training such individuals themselves in problem-solving skills may be a particularly useful approach in helping family caregivers to cope more effectively, given the distress that can result from the day-to-day care of cancer survivors [105]. A large-scale RCT of 476 dyads (patients with advanced cancer and caregivers) compared a problem-solving intervention to treatment as usual in both survivors and caregivers [106]. While caregivers who received a problem-solving intervention in that study experienced a decline in quality of life, it was at less than half the rate of the decline in quality of life experienced by those who did not receive an intervention.

Problem-solving interventions appear to be helpful for both cancer survivors and their caregivers. The evidence for PST for caregivers in particular appears to be more compelling than CBT for caregivers. This may reflect the fact that the distress that accompanies cancer is based on realistic and possible concerns, where problem-solving may be a more effective approach than trying to alter the cognitions related to distress. However, further and more current studies are needed to continue to establish the effectiveness of problem-solving interventions.

9.8.4 Mindfulness-Based Stress Reduction

Mindfulness-based stress reduction (MBSR) has been used to help cancer survivors cope with many of the common posttreatment problems detailed above. Mindfulness itself stems from Eastern meditation practices and has been described as non-elaborative, 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. Attempts at a definition have resulted in a two-component model of mindfulness, including self-regulation of attention on the present moment and an attitude of openness and acceptance [107], and a three-component model, which includes the same elements as the two-component model in addition to intention, directed toward practice [108]. Mindfulness is cultivated by practicing various forms of meditation, or mental training, which can be performed in formal meditation sessions, or during day-to-day activities, such as washing the dishes.

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 [109, 110]. 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 45 min of daily home practice and a 6-hour silent retreat between weeks 6 and 7.

MBSR was adapted by Carlson and Speca into Mindfulness-Based Cancer Recovery (MBCR), a modified program similar to MBSR, considering the unique needs of cancer survivors [111]. For example, sessions are shorter (1.5 h) due to high levels of functional impairment, weakness, and fatigue participants can experience, many of whom are on active treatment. A principle aspect of mindfulness meditation that has particular salience for cancer patients is the "here and now" orientation. Some sources of stress for cancer patients relate to the past (e.g., attributions about cancer causation, regrets about past decisions or life priorities) or concerns about the future (e.g.,

enduring pain or the loss of life itself). The practice of mindfulness provides an effective antidote to these sources of stress 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.

The frank uncertainty of cancer challenges pre-existing perceptions of personal control over one's future and one's own body, which can be strongly associated with psychological distress and diminished psychosocial adjustment to cancer [112, 113]. MBSR addresses these factors in several ways. Adopting the attitude and practice of acceptance frees patients from unrewarding efforts to control the uncontrollable. 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.

There is strong evidence for the effectiveness of MBSR for improving psychological outcomes among cancer survivors specifically. MBCR, adapted by Carlson and Speca, has been examined in several studies and has resulted in reduced mood disturbance, tension, depression, anger, concentration, distress, anxiety/fear, physical symptoms (e.g., peripheral stress, cardiopulmonary, gastrointestinal), and stress-related behaviors [114]; improved quality of life, sleep [115], social support, cortisol profiles [116], and maintained telomere length [117]. Improvements have been documented to last for up to a year post-intervention [118]. Currently, several systematic reviews and meta-analyses support improvements from a variety of MBSR adaptations on quality of life, mood, distress [74], stress [75, 76], depression, anxiety [75, 77–80], mindfulness skills [78], fear of recurrence, fatigue, and emotional well-being [79] for cancer survivors. Several studies have also supported changes in biological measures such as cortisol and inflammatory markers [81, 82] and cytokines.

Recently, the Internet has been explored as an avenue for delivery of mindfulness programs to cancer survivors. Zernicke et al. compared online MBCR to a waitlist control group in a RCT of 62 cancer survivors, reporting moderate effect size improvements in mood disturbance, stress, spirituality, and mindfully acting with awareness in the MBCR group [119]. Everts et al. reported promising pilot results for an online mindfulness-based cognitive therapy program to reduce cancer-related fatigue [120].

Overall, MBSR and MBSR adaptations have been repeatedly demonstrated as effective for a myriad of psychological outcomes for cancer survivors. Consequently, use of MBSR in the context of psychosocial oncology is deemed supported by the highest level of evidence [121].

9.9 Future Directions

Future areas for consideration include more rigorous methodology, generalizability of treatment effectiveness, exploration of diverse delivery modalities, and assessment of health economic outcomes. Regarding methodological rigor, future studies should strive to standardize treatment delivery according to protocols and include measures of treatment fidelity to ensure that survivors are receiving the treatment in a way consistent with how it was initially developed and tested. Otherwise, it is difficult to discern whether null trials are due to ineffectiveness of treatments or just suboptimal treatment delivery. Use of multimodal assessment (e.g., corroboration of self-report and objective measures, such as self-reported psychological distress and salivary cortisol, a stress marker) will continue to build the strength of the evidence and render it more compelling. Although blinding of participants is difficult, if not impossible to accomplish in intervention studies, outcome assessors should be blinded when possible, and researchers should be blinded to group allocation before participants have been recruited to studies. Additionally, reporting of procedures and outcomes should be as explicit as possible. Particularly when interventions are not manualized, they should be adequately described to enhance replicability and help delineate the effectiveness of specific treatment components. Reviews of individual treatment components, if possible, may help

determine the most effective components of unstandardized treatments.

Regarding the specificity of treatment effectiveness, more research is needed to understand what types of interventions are effective for which individuals, with which types of cancer, which stage of cancer, what level of distress, and with what demographic characteristics. For example, while the effectiveness of these interventions for breast cancer survivors has been well-studied, future studies should examine whether interventions are effective for other types of cancer (e.g., types that may result in more functional limitations such as head and neck and brain). Conducting more large-scale studies including survivors of several types of cancer and conducting stratified analyses to see if treatments are equally effective for these different groups could do this. Additionally, several studies employ interventions that include several different treatment components. More dismantling studies should be conducted to discern which active components of treatment are most effective for which outcomes. Currently, the majority of studies compare interventions to control groups. Future studies should consider comparing interventions to active control groups or other established interventions to 1) delineate observed effects that are a function of the intervention itself beyond time, expectancy effects, or attention and 2) explore the relative effectiveness of different interventions. Finally, future studies could consider treatment preferences. Results from a study of distressed breast cancer survivors by Carlson et al. suggest that those who receive their preferred intervention may show greater improvements in psychological outcomes than those who do not [122]. Thus, considering treatment preferences may improve ecological validity, as survivors in the real world would only seek therapies they are interested in.

Regarding delivery, future studies should examine alternative methods of treatment access and implementation, such as tele-health, online interventions, and mobile applications. There are several potential advantages to conducting assessments and/or delivering interventions remotely, including improved access to services (e.g., among those living in remote areas, with limited mobility, or of lower socioeconomic status), improved cost-effectiveness, increased flexibility, and standardized delivery of treatment [123]. For cancer survivors who may have busy schedules due to frequent appointments or who are avoiding groups of people due to compromised immune systems, remote delivery of services could be particularly beneficial. Drawbacks to remote delivery of services include potential issues with security, questions about how legal and ethical regulations apply to remote delivery of services, and potential for missing important nonverbal information when interacting with clients [123]. Another alternative method for symptom monitoring may entail online portals linked with electronic medical records where health-care providers can monitor survivors' distress and provide referrals accordingly. Future research should continue to examine the effectiveness of remotely delivered interventions compared to their in-person counterparts, as well as the acceptability of these interventions to both survivors and health-care providers.

Finally, the collection of health economic information such as intervention costs and potential downstream cost savings or cost increments to health care can be helpful in guiding allocation of future resources. While there is ample evidence to support efficacy and effectiveness of psychosocial interventions for psychological outcomes among cancer survivors, the lack of data on the cost-effectiveness of these interventions can prevent them from being widely implemented [124]. In 2016, Dieng and colleagues reviewed economic evaluations of psychosocial interventions in cancer, concluding that psychosocial interventions were generally cost-effective [124]. However, this review was only based on eight studies, with considerable variability in the interventions (e.g., both individual and group; CBT, supportive-expressive therapy, educational programs). A 2011 review of the cost-effectiveness of psychosocial interventions for treating anxiety and depression in cancer survivors reported that results were mixed and evidence was inconclusive, but that psychosocial interventions were relatively inexpensive [125]. Further

studies are needed to establish the cost-effectiveness of psychosocial interventions, as well as compare the relative cost-effectiveness of different interventions.

These future directions will continue to work toward determining optimal content and delivery of psychosocial evaluation and, if necessary, intervention, with the primary goal of promoting quality of life and well-being for cancer survivors.

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Pain

10

Victor T. Chang and Neena Kapoor-Hintzen

10.1 Introduction

Pain in cancer survivors is increasingly recognized as an important problem [1, 2]. Cancer-related pain may be pain from the cancer itself or pain related to cancer treatments. Reasons for interest in this area include the large and growing number of cancer survivors, the complexity and scope of pain problems encountered by cancer survivors, and the effect of pain on quality of life and function. Many care providers for cancer survivors are not pain specialists and may not be familiar with the assessment and management of cancer-related pain. There are two major groups of cancer survivors who experience pain:

1. Patients with advanced or metastatic cancer that has been controlled but is likely to recur in the future. For these patients, management of ongoing chronic pain, cancer treatment-related pain, and cancer pain may all be relevant problems. Progression of disease must be taken into account when new pain is experienced. As prognosis is often poor, the time horizon for the management of pain is shorter for these patients.
2. Patients who have undergone a curative or likely curative procedure, where cancer recurrence or progression may not be a significant concern for the near future. Concurrent chronic pain and/or cancer treatment-related pain is the main focus, though relapse and second malignancies must remain in the differential for new pain. The time horizon for the management of pain can be prolonged. As survivors may transition out of oncology settings, they are more likely to be encountered by primary care providers.

For the purpose of this chapter, we will focus on the second group of patients. Our goals are to review and provide an update on many of the issues pertaining to evaluation and management of pain among cancer survivors and provide recommendations that may be useful for clinical care.

10.2 Epidemiology of Pain in Cancer Survivors

The prevalence of pain in survivors of cancer is estimated to be 40% [3]. While it is recognized that cancer patients experience pain, the extent to

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which they report persistent pain compared to the general population was recently reported in an analysis of the 2010 US National Health Interview Survey. In this study, the prevalence of symptom phenotypes was compared between 604 adult cancer survivors (most of whom were over 5 years post-diagnosis) and 6166 non-cancer individuals. The authors found that survivors had a higher prevalence of pain (73.5% in survivors vs. 56.6% $p < 0.01$, OR 2.1, 95% CI 1.7–2.6), a difference that remained statistically significant after adjusting for covariates. Having a chronic condition significantly increased the likelihood of experiencing pain, and women were more likely to have pain. Pain had the greatest effect on health-related quality of life, followed by fatigue, depressive symptoms, and cognitive disturbance. However, the increased symptom burden, including pain in cancer survivors, could not be explained by the presence of chronic conditions alone, leaving room for other causes, such as treatment exposures. These findings highlight important clinical concerns including treatment toxicity, age, and comorbidities [4].

10.2.1 Pain Affects Cancer Survivors in All Age Groups

In a survey of 9535 survivors of childhood cancer from the Childhood Cancer Survivor Study, the prevalence of pain attributed to cancer or its treatment was 10.2%. Patients at increased risk for pain included those aged greater than 24 years at interview, income under $20,000/year (OR = 1.8, 95% CI = 1.5–2.1), education level of high school or lower (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). Patients with a diagnosis of Hodgkin's disease were at decreased risk (OR = 0.7, 95% CI = 0.6–0.9) for pain. Those who had received radiation therapy had an increased odds ratio varying from 1.5 to 3.4 depending on the region radiated. Chemotherapy and surgery were not predictive of pain. The authors noted the difficulty in evaluating somatic complaints as a significant percentage of survivors of sarcomas and bone tumors also experienced cancer-related anxiety and various fears, which can exacerbate pain [5]. In an analysis of 16,079 childhood survivors at least 5 years from diagnosis, a high symptom distress cluster was identified in 11% of survivors that was associated with poor reported health, headaches, and bodily pain [6].

Among 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). The most common symptom was pain, present in 31% and attributed to cancer by 21% of those 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. Of those who reported pain, pain was attributed to cancer by 29% of those with breast cancer, 11% of those with colorectal cancer, and 11% of those with prostate cancer. The number of years since diagnosis was inversely correlated to the patients associating the pain to cancer, and the number of symptoms was correlated both with the number of types of treatments and with having received chemotherapy [7]. In another survey of 964 older cancer survivors with 10 cancers 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%, $p < 0.005$) [8].

10.2.2 Pain Affects Cancer Survivors at All Stages of Cancer Survivorship

Longitudinal studies show there are subsets of cancer survivors whose clinical course is dominated by pain. For example, in a study of 4903 survivors at 1 year after diagnosis, a high symptom burden cluster was identified for 1399 (28%) with the remainder in a low symptom cluster. The high symptom cluster group had lower quality of life. The most important symptoms in this cluster were pain, fatigue, and depression. Risk factors included both disease-related variables (lung

cancer, metastatic cancer, receiving chemotherapy, number of comorbid conditions) and socioeconomic variables (unemployed, lower education, lower income, younger age) [9].

For adult long-term survivors, a systematic review found a significant subset of cancer survivors who experienced severe levels of pain, fatigue, and depressive symptoms up to 10 years following cancer [10]. In another analysis of adult childhood survivors with an average of 16 years following diagnosis, survivors were significantly more likely than their siblings to report pain sensations, migraine, and frequent headaches; the prevalence of pain was 12.3% compared to 6.3% in siblings [11]. These studies suggest that conditions frequently associated with pain in various groups of cancer survivors regularly include medical comorbid conditions, such as obesity, younger age, female sex, and race, and social/economic conditions, such as lower education levels, lower income, absence of social support, and language proficiency.

10.2.3 Pain Affects Cancer Survivors' Quality of Life

Pain can cause distress and interfere with function and quality of life (QOL). In one study of cancer survivors, the presence of cancer-related chronic pain was associated with decreased functioning in five of six scales of the European Organization Research Treatment Cancer QLQ-C30 and was associated with female sex and African-American ancestry [12]. In other studies, some groups of survivors reported worse quality of life, while others had QOL similar to controls. Possible explanations for a lack of a consistent association include the small fraction of survivors with severe pain, use of quality of life questionnaires that may not always capture pain [13], and that an individual's overall symptom burden may be insufficient to affect quality of life [14].

The relationship of pain to employment in cancer survivors remains inconclusive. Fatigue may be a stronger symptom predictor of employment [15], and pain severity by itself may not predict disability [16]. In one study of over 2000 colorectal cancer survivors at 1 year follow-up, the presence of moderate to high pain interference was significantly associated with no longer having a job at follow-up among previously employed survivors [17].

10.3 Pathophysiology of Pain and Management Approaches

There are several sources of pain or pain mechanisms including pain pathways, neuropathic pain, nociceptive pain, bone pain, myofascial pain, and visceral pain. The following section provides an overview of these various sources of pain.

10.3.1 Pain Pathways

Pain signals, or nociceptive signals, are transmitted from the periphery to the dorsal horn of the spinal cord and, from there, to the brain by ascending pathways. The role of the spinal cord neurons and glial cells in modulating signal transmission is an area of current research. Procedural interventions attempt to surgically block or decrease transmission of nociceptive signals in ascending pathways. Descending pathways from the brain to the spinal cord can inhibit or facilitate pain transmission at the spinal cord level. The role of descending pathways as a modulator of pain is also an area of active research. Pharmacological interventions can affect either ascending or descending pathways. Morphine affects the ascending pathways by binding to mu-opioid receptors in the dorsal horn and activates the descending tracts from the locus coeruleus and the rostral ventral medulla that project to the spinal cord by binding to brainstem receptors. The descending tracts rely on adrenergic and serotonergic transmission, and activation of the descending adrenergic pathway by tricyclic antidepressants, or by serotonin-norepinephrine reuptake inhibitors (SNRI) such as venlafaxine or duloxetine, can provide analgesia. The spinal cord neurons and glial cells and the descending tracts are thought to be important in the

development and maintenance of chronic pain conditions [18].

10.3.2 Neuropathic Pain

Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system either at peripheral or central levels [19]. Making a diagnosis with high probability requires history, distribution of pain in the territory of a nerve, a physical examination with positive and negative sensory findings with attention to allodynia and hyperalgesia, and appropriate diagnostic testing. An important concept in neuropathic pain is central sensitization, whereby changes in the spinal cord lead to prolongation of pain transmission. The prevalence of neuropathic pain in cancer patients has been estimated to range from 20% to 40% [20]. Three commonly encountered types of neuropathic pain – postsurgical pain syndromes, phantom pain, and chemotherapy-induced peripheral neuropathy (CIPN) – are covered later in the chapter.

10.3.3 Nociceptive Pain

Nociceptive pain is related to tissue damage. The most significant comorbid nociceptive pain condition is musculoskeletal pain, a term that usually encompasses osteoarthritis, low back pain, rheumatoid arthritis, and osteoporosis [21]. Bone metastases and arthritic syndromes share the mechanisms of increased cytokines and stimulation of skeletal nerve growth by disease [22, 23]. Spinal stenosis with foraminal narrowing represents an important type of arthritic pain that can be confused for bone metastases and epidural cord compression. Patients with spinal stenosis may complain of back pain, radicular pain, and pain that is worsened by walking. Differentiating features are that spinal stenosis pain is relieved by lying down, whereas lying down increases epidural disease, and that myelopathic findings are not present on physical examination with spinal stenosis.

10.3.4 Muscle Pain

Muscle pain can present as tense muscles, cramps (brief contractions) or spasms (sustained contractions), or as myofascial pain, a form of muscle pain with taut bands in addition to areas of tenderness called trigger points. Patients with deconditioning are at risk for muscle pain. Muscle pain may be a component of postsurgical pain syndromes and low back pain.

10.3.5 Visceral Pain

Visceral pain arises from internal organs and is likely to be present in patients with abdominal or pelvic complications of cancer or its treatment. Visceral pain is often poorly localized and may be accompanied by referred pain to other parts of the body, symptoms such as nausea and vomiting, and can sometimes be sharp from inflammation of the organ capsule [24].

10.4 Cancer Treatment-Related Pain

10.4.1 Surgery

Persistent post-surgical pain is pain that develops after surgery, duration of at least 2 months, location in the territory of the surgery, and with exclusion of other causes. During surgery, nociceptive stimulation leads to a barrage of C fiber impulses that activate the spinal cord receptors and result in the development of central sensitization and a clinical hyperalgesic state [25]. Inflammation at the surgical site, nerve damage, and other mechanisms can also contribute to persistent postsurgical pain [26].

Chronic postsurgical pain syndromes are now recognized as a distinct clinical entity with an overall incidence that depends on the surgery performed [27]. In a systematic literature review, incidence ranged from 6 to 60%, with the highest rates reported for breast and thoracic surgeries and amputations [28].

Amputation In a national survey of 105 survivors who had undergone amputation of extremity sarcomas and soft tissue tumors, 95 reported pain as mild in 46 (48.4%), moderate in 32 (33.9%), and severe in 9 (9.5%); interference was absent in 13 (14%), mild in 46 (49%), moderate in 18 (19%), and severe in 17 (18%). Pain was described as phantom pain or stump pain [29].

Phantom Pain Phantom pain is defined as pain referred to a surgically removed limb or a portion thereof [30]. Traditionally associated with limbs, phantom pain has been reported for resected internal organs such as the stomach, rectum, uterus, and bladder [31–33] and in patients with breast cancer [34]. Phantom pain should be differentiated from stump pain (mechanical pain) and phantom sensations (not painful). Phantom pain is highly prevalent but not always severe, and severity may vary considerably over time [35]. Levels of postoperative pain and catastrophizing may be risk factors for phantom pain [36]. Worsening phantom limb pain after a period of stable pain should raise suspicion for a new malignancy [37–39].

Post-radical Neck Dissection Syndrome 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 ranges from 30% with neck pain and 70% with shoulder pain. 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 [40]. In another series, 30% had neck pain, and 37% had shoulder pain; neuropathic, myofascial, and joint pain components were also identified [41].

Postmastectomy Pain Syndrome (PMPS) In this syndrome, pain is reported immediately or soon after any type of breast cancer surgery including mastectomy or removal of a lump. Pain affects the anterior thorax, axilla, and/or medial upper arm [42]. Pain is typically described as shooting, aching, or burning, with allodynia and hypoesthesia on examination. Postmastectomy pain can also be experienced by women who have undergone only lumpectomy without axillary dissection and with sparing of the intercostobrachial nerve [43]. Postmastectomy pain may include a variety of pain syndromes, including neuropathic pain, phantom breast, rotator cuff dysfunction, and myofascial pain [44]. Pain in the mastectomy site that progresses or has atypical features should lead to assessment for infection or tumor recurrence [45].

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 [46]. At 6 months out from surgery, in a prospective cohort of 174 patients, the incidence of pain syndrome was 52%. Risk factors included age less than 40 years and those who were submitted to axillary lymph node dissection (with more than 15 lymph nodes excised) [47]. At 1 year from surgery, in a prospective cohort of 537 patients, of 475 (88%) available for analysis at 1 year, the prevalence of pain was 42%, moderate to severe pain at rest was 14%, and during movement was 7% [48]. In another group of 116 women followed for 1 year after surgery, the most common causes of pain were myofascial pain syndrome in 52 patients and axillary web syndrome in 56 patients. The shoulder girdle muscles were most commonly affected [49]. At 2–5 years out from surgery, in a survey of 833 patients, 41% reported pain, of which 51% had mild, 41% moderate, and 8% severe pain. Among the women who experienced pain, 33.8% reported symptoms and signs of neuropathic pain [50].

A survey of 2000 breast cancer survivors who were at least 5 years from treatment indicated that 42% reported pain and 29% reported pain from cancer with common sites the breast including shoulder, axilla, and chest. The incidence of pain in controls was 32% [51]. In a follow-up study at 9 years from surgery of 138 survivors who had reported pain, with responses from 113

(82%), 59 (52%) reported resolution of their postmastectomy pain syndrome. Patients with persistent pain had significantly decreased quality of life compared to those whose pain had resolved. However, for women with persistent PMPS, SF-36 scores had improved over time [52]. A study of 159 women with median 19 years follow-up who had received breast conserving surgery followed by 3-D conformal radiation found that 15% complained of moderate to severe breast pain [53]. A systematic review found that risk factors for persistent postsurgical pain were younger age, radiotherapy, axillary lymph node dissection, greater acute postoperative pain, and preoperative pain [54].

Post-thoracotomy Pain Syndrome In this syndrome, pain recurs or persists along a thoracotomy scar at least 2 months following the surgical procedure [55]. The prevalence varies, but 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 [56]. Pain at postoperative day 1 is predictive of pain 1 month and 1 year after thoracotomy [57]. Physical examination 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.

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 reported to healthcare professionals. In one review, the incidence of lymphedema in breast cancer patients ranged from 6% to 30% [58]. In a cohort of 263 breast cancer survivors who had undergone axillary dissection 20 years prior, 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 [59]. 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 [60]. Pain from lymphedema is also associated with significant psychological distress [61, 62]. In addition to upper arm lymphedema, as reported in breast cancer survivors, lower limb lymphedema must also be considered.

In a survey of 487 women who had been treated for gynecologic malignancies, a diagnosis of lower limb lymphedema was made in 89 (18%). Of the 89 with lymphedema, 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. Symptoms were generally managed with compression garments, physical therapy, and changes in clothing, information received, and changes in body image [63]. Another survey of 802 gynecologic cancer survivors found that 10% had been diagnosed with lymphedema and an additional 15% had unreported symptomatic leg swelling [64].

10.4.2 Radiation

The hallmarks of long-term radiation toxicity are fibrosis, atrophy, and telangiectasias. While molecular mechanisms are incompletely characterized, damage to the normal tissue and microvasculature leads to repair processes that persist over time, sometimes decades. Muscle fibrosis and demyelinization of nerve fibers as a long-term complication may also be important in the development of radiation-related pain syndromes Table 10.3. Pain can generally result from effects of radiation on neural tissue, muscle, vasculature, or entrapment of nerves by fibrosis. With improvements and new radiation techniques, the spectrum of radiation-related pain syndromes may change in the future.

Neck Syndromes Hodgkin's lymphoma survivors who have received mantle field radiation may develop weakness of neck extensor muscles, experience difficulty maintaining neck posture, and experience secondary neck pain; shoulder girdle muscles may also be affected [65].

Cervical dystonia, also known as spastic torticollis, is seen in patients who have received radiation for head and neck cancers and for brain tumors [66]. In one survey, two thirds of patients with cervical dystonia reported chronic pain in the neck or upper back, with involvement of the ipsilateral head and arm [67].The term radiation fibrosis syndrome has been proposed to encompass symptoms that result from radiation of the neck in patients with head and neck cancer or Hodgkin's lymphoma [65].

Brachial Plexopathy This condition has been seen more frequently in patients with breast cancer and in some patients with lung cancer and Hodgkin's lymphoma. Risk factors for plexopathy in breast cancer patients include higher doses of radiation, radiation technique, and administration of chemotherapy. A key feature of this complication is delayed onset. In one study, patients presented with symptoms at a median of 1.5 years after treatment with a range of 3 months to 14 years; pain was the first symptom in 29% of the patients [68]. In one larger study of 150 patients, long-term effects and onset of symptoms presented at 30 years after radiation [69]. 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 [70].

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 [71]. The syndrome may be difficult to distinguish from recurrent tumor or radiation-induced malignancy. MRI with contrast is the recommended modality for imaging; PET-CT scans can identify extent of tumor involvement and help with distinguishing radiation plexopathy from tumor plexopathy but only provide limited imaging of the plexus [72].

Radiation Enteritis Radiation enteritis, or diarrhea in patients who received radiation to the pelvis, can occur along with up to 23 other lower gastrointestinal symptoms. Approximately 40% of patients experience moderate or severe pain in the abdomen, back, rectal, perianal, or anal areas; diagnoses include small intestinal bacterial overgrowth and bile acid malabsorption [73]. Patients may try to manage on their own and often wait a long time before bringing this symptom up with physicians [74]. Radiation enteritis may comprise a number of different gastroenterological diagnoses that can be evaluated with an algorithm [75].

Radiation Pelvic Disease The term radiation pelvic disease has been used to denote problems encountered by patients with colon, rectal, urologic, and gynecologic cancers that have received pelvic radiation as part of their cancer treatment. The spectrum of symptoms can include the gastrointestinal and urologic tracts and lower extremity lymphedema. In one survey of 616 survivors of gynecologic cancers treated with radiation at a median of 7.6 years, compared to 344 controls, survivors had an increased risk of pain in the pubic bone (RR 10.3, 95% CI 4.0–26.7), dyspareunia (RR 3.7, 95% CI 2.4–5.7), lower abdominal pain, and multiple other symptoms [76].

Sacral insufficiency fractures can present as low back, buttock, groin, or hip pain in patients who received pelvic radiation or chemotherapy with radiation. Usually associated with cervical cancers, fractures have also been reported in patients with anal cancer [77], prostate cancer [78], rectal cancer [79], and chordomas [80]. Risk factors are age greater than 50 years, female sex, and lower body mass index. Time of

onset ranges from 2 months to 8 years after radiation with a median incidence occurring at 6–20 months [81]. Where the diagnosis is made on the basis of radiographic chart review, approximately half of patients are symptomatic. Median duration of pain in one report was 22 months [80].

Diagnosis is usually made by computed tomography. Additional fractures may also be found [82]. Sacral insufficiency fractures have a mildly elevated standardized uptake values (SUV) on PET scans and may be mistaken for metastases [83].

Radiation Lumbosacral Plexopathy Lumbosacral plexopathy has been reported in patients who received radiation for prostate, testicular, or gynecological cancer. The median time to onset of symptoms is 5 years [84]. 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 [85, 86]. The differential diagnosis must include the recurrence of cancer.

Osteoradionecrosis Osteoradionecrosis results from radiation effects on the blood vessels and presents as exposed nonhealing bone in a radiated area. Osteoradionecrosis of the mandible is most well known; other sites include the temporal bone [87], cervical spine [88], and pelvis [89] with presentation years later. Prevalence in head and neck cancer patients varies from 5 to 7% regardless of treatment modality. Risk factors include radiation dose greater than 6000 cGy and poor dentition [90]. It is recognized as a painful condition.

10.4.3 Chemotherapy

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect of multiple chemotherapy agents and can have significant long-term impact [91, 92]. Initial symptoms are sensory including paresthesia (numbness and tingling) and dysesthesia (burning, shooting, throbbing, stabbing sensations), in a stocking and glove distribution, and can progress to a chronic neuropathy. Additional symptoms described include dropping items, gait impairment, orthostatic symptoms, and falls [93, 94]. Some agents (vincristine) can lead to autonomic neuropathy. For taxanes and oxaliplatin, an acute pain syndrome can predispose to a chronic pain syndrome. These symptoms can impair a patient's ability to complete activities of daily living, cause severe debility, and interfere with ability to complete treatments. The use of combination regimens in diseases such as breast cancer, head and neck cancer, lung cancer, and multiple myeloma is accompanied by higher rates of CIPN. Symptoms are sometimes reversible but can persist for years and even worsen over time, a phenomenon called coasting. Chemotherapy agents associated with CIPN include cisplatin, oxaliplatin, taxanes, vincristine, bortezomib, and thalidomide [95].

The biological basis for the development of peripheral neuropathy is puzzling as nerves are not cells that routinely divide. Current lines of study include examining the effect of chemotherapy agents on mitochondrial DNA, important in transport of substances in a peripheral nerve, and of damage from inflammation secondary to chemotherapy [96]. Pharmacogenetic studies are under way to identify the association of various single nucleotide polymorphisms with the development of CIPN [97]; one study found that genetically determined African-American ancestry itself was a risk factor for taxane-induced neuropathy [98].

10.4.4 Hormonal Therapy

Steroids Osteonecrosis is seen in survivors of childhood acute lymphoblastic leukemia, typically 2 years post-diagnosis, with increased risk among those who received bone marrow transplants and patients who are older than 10 years at diagnosis. Multiple joints may be affected,

with the most common sites being the hip and knee, followed by the shoulder and ankle [99]. Diagnosis is made using magnetic resonance imaging. In a survey of 943 survivors of childhood leukemia evaluated with the SF-36, patients with symptomatic osteonecrosis had markedly lower scores for general health, physical functioning, and bodily pain [100]. In an analysis of 1409 children with ALL on Children's Cancer Group protocol CCG-1882, symptomatic osteonecrosis had been diagnosed in 111 (9%) at 3 years. Pain required opioid analgesics in 50 (47%), and 46 (44%) of patients were restricted to wheelchair or bed rest. Symptoms were ongoing in 83% of patients, and orthopedic procedures had been performed in 27 patients with an additional 23 procedures planned [101].

Aromatase Inhibitor Musculoskeletal Syndrome Aromatase inhibitor (AI) musculoskeletal syndrome refers to joint pain and/or stiffness, low back pain, or myalgias that develop after starting treatment with aromatase inhibitors. Typically occurring within the first 6 weeks of treatment, symptoms may develop up to 1 year later [102]. When severe, this syndrome is associated with discontinuation of aromatase inhibitors by patients. In the ELPH study, 156 (32%) of patients had discontinued AI therapy at 24 months, with 24% because of musculoskeletal toxicity [103]. The etiology of these symptoms is unclear. Current investigations have examined the role of cytokines, and pharmacogenetics approaches to obtain clues [104–106].

Atrophic Vaginitis Estrogen deprivation can contribute to the onset of atrophic vaginitis or worsen existing symptoms. Associated genitourinary symptoms include vaginal dryness, dyspareunia, itching, burning, soreness, and discharge [107].

Fractures Both estrogen deprivation therapy (breast cancer) [108] and androgen deprivation therapy (prostate cancer) are associated with the development of osteopenia and an increased risk for fractures [109].

10.4.5 Stem Cell Transplantation

In a survey of 454 long-term adult onset survivors of stem cell transplantation, survivors were more likely to experience musculoskeletal pains and joint problems than controls [110]. Patients with ongoing active chronic graft vs. host disease (GHVD) are likely to be symptomatic. In a survey of 584 survivors more than 2 years out from transplant, those with active GHVD were more likely to experience pain with an odds ratio of 4.2 (95% CI 2.4–7.1) with a prevalence of 40% [111]. The most frequent sites of pain are the skin, mouth (ulcers) [112], eyes (painful dry eyes from ocular GVHD [113]), and mucosa (vagina, glans penis). The presence of chronic pain and patient reported severity of current GHVD were independent predictors of depression and fatigue in allogeneic transplant recipients [114].

10.4.6 Medication-Related Osteonecrosis of the Jaw

Osteonecrosis of the jaw was originally reported with intravenous bisphosphonates and denosumab. It is now also associated with oral bisphosphonates and with tyrosine kinase inhibitors (sunitinib, sorafenib), mTor inhibitors (sirolimus), and a monoclonal antibody to the vascular endothelial growth factor receptor (bevacizumab). Overall risk varies between 0.1% and 7% depending on the agent. Tooth extractions and dental procedures are risk factors for developing osteonecrosis of the jaw [115].

10.5 Pain Assessment and Management

It is important for the clinician to make certain that the patient receive a comprehensive pain assessment either within the initial visit and generate a referral to a pain specialist for more complex cases. Table 10.1 provides a quick summary of various pain symptoms commonly experienced by survivors by primary cancer sites.

Table 10.1 Examples of pain symptoms and syndromes by cancer primary site

Primary site	Pain syndrome
Brain [116]	Headache
Head neck	Neck and shoulder pain – myofascial, radiation fibrosis
	Post-radical neck dissection pain syndrome
	Chemotherapy-induced peripheral neuropathy (taxanes and cisplatinum)
Thyroid [117]	Cramps and arthralgias
Breast	Phantom breast
	Postmastectomy pain
	Lymphedema
	Shoulder and arm dysfunction
	Joint pains and stiffness (aromatase inhibitor)
	Atrophic vaginitis/ dyspareunia Chemotherapy-induced peripheral neuropathy (taxanes)
Lung	Post-thoracotomy pain syndrome
Liver	Chronic pain from liver lesions
	Post embolization pain
Colorectal	Proctitis
	Pain and numbness in hands and feet (oxaliplatin chemotherapy) Pain due to adhesions
Anal [76, 118, 119]	Perianal paresthesia
	Phantom anus Radiation proctitis
Germ cell tumor	Peripheral neuropathy – cisplatin
	Raynaud's syndrome
Prostate cancer	Bone pain (compression fractures)
	Pelvic symptoms from radiation
GYN Tumors [76]	Chemotherapy peripheral neuropathy (platinum/taxanes)
	Lymphedema legs
	Dyspareunia; genital pain
	Painful bowel movements – radiation enteritis
	Pelvic bone pain
Childhood leukemia	Peripheral neuropathy
	Long bone/joint pain
Multiple myeloma	Peripheral neuropathy (chemotherapy – bortezomib, thalidomide)
	Painful neuropathy (myeloma)
	Bone pain (compression fractures)
Sarcoma	Phantom pain
	Stump pain
	Pain interference

10.5.1 Barriers to Assessment

Both the National Comprehensive Care Network and the American Society of Clinical Oncology recommend assessment for pain at every visit; however the comprehensive assessment of pain can vary from a simple visual analogue assessment of pain severity or numerical rating, to more extensive assessment. The importance of assessing pain is highlighted by an analysis from the American Cancer Society, in which 5165 of 9170 (56%) survivors at 2, 5, and 10 years out reported pain from cancer or its treatment. Of these, 4707 completed questionnaires that asked respondents if they had encountered common patient-level, provider-level, and system-level barriers to pain management, and 75% of all survivors indicated at least one barrier. The most common patient-level barriers were reported as "not considering pain bad enough to seek treatment" (37%) and "preferring not to treat pain with medicine" (37%). The most common provider-level barrier was the "doctor not asking about pain" (16%) [120]. Underestimation of patient symptoms in cancer patients by providers is well documented [121, 122] and represents another important barrier. Reasons for this underestimation include patient perceptions of communication with physicians [123], differing perceptions of what constitutes symptom severity, and clinic time available for symptom assessment. This limited communication leads to less optimal symptom assessment and management.

10.5.2 Pain Assessment

Pain assessment includes assignment, where possible, of an underlying pain physiology and pain diagnosis. When evaluating pain in cancer survivors, a differential diagnosis includes:

- Pain resulting from damage caused by the original tumor.

- Pain from treatment-related toxicity (e.g., surgery, radiation, chemotherapy) or other procedures. 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 nonmalignant disease.
- Pain from comorbid non-cancer conditions (other chronic pain).

Additional information gathered during a pain assessment might include:

(a) The presence of additional symptoms – The recognition that cancer patients and cancer survivors have multiple symptoms has led to the development of multiple symptom assessment [124]. Identification of groups of symptoms could simplify assessment and possibly identify common etiologies and treatment strategies [125]. When asking about pain in cancer survivors, it may be helpful to ask about concurrent fatigue, difficulty sleeping, and depression/mood. It is important to highlight that a diagnosis of depression should not be made in the presence of severe unrelieved pain.
(b) Patient perceptions of pain severity, distress, interference, and pain relief from interventions renumber the other comments.
(c) Ability to function physically and during the day and perceived ability to get involved in activities despite pain.
(d) Psychological assessment for catastrophizing, for self-efficacy, and for interest in self-management approaches to pain.
(e) Presence of comorbidities that may affect pain assessment. Modifiable conditions can include other painful conditions (e.g., arthritis), mental health disorders, tobacco and alcohol use, obesity, and nutritional status [126].
(f) Family and social support networks.
(g) Previous experiences with pain and pain medications.
(h) Physical examination findings regarding the site(s) of pain, with attention to localized tenderness, sensory abnormalities such as allodynia and hyperalgesia, and decreased mobility. Allodynia refers to a non-painful stimulus being perceived as painful.

10.6 Pain Management Approaches

10.6.1 Barriers to Pain Management for Cancer Survivors

A common barrier to effective management of pain among cancer survivors is the lack of clearly identifying who is responsible for managing pain in cancer survivors. Issues include transition of patients between oncologists and primary care providers, changes necessitated by changes in the patient's status, and differences in practice and prescribing patterns.

An analysis from the American Cancer Society found as well as the patient and provider-level barriers mentioned under assessment indicated that the most common system-level barrier was "health insurance not paying for pain medications." Patients from minority groups, with less education, more comorbidities, older age, and concurrent anxiety or depression, were significantly more likely to encounter barriers to pain management [120].

10.6.2 Biopsychosocial Approach

The biopsychosocial model recognizes that in addition to biomedical care, social and psychological factors can affect pain and outcomes of pain management. There is general agreement that management of chronic pain should follow a biopsychosocial model of pain (Fig. 10.1). In this treatment approach, there are five components – psychological assessment and acceptance commitment therapy, graded exercise program, nutritional program for weight loss if needed, pharmacological therapy, and social support [127–129]. This multimodal approach is an important component of the National Pain

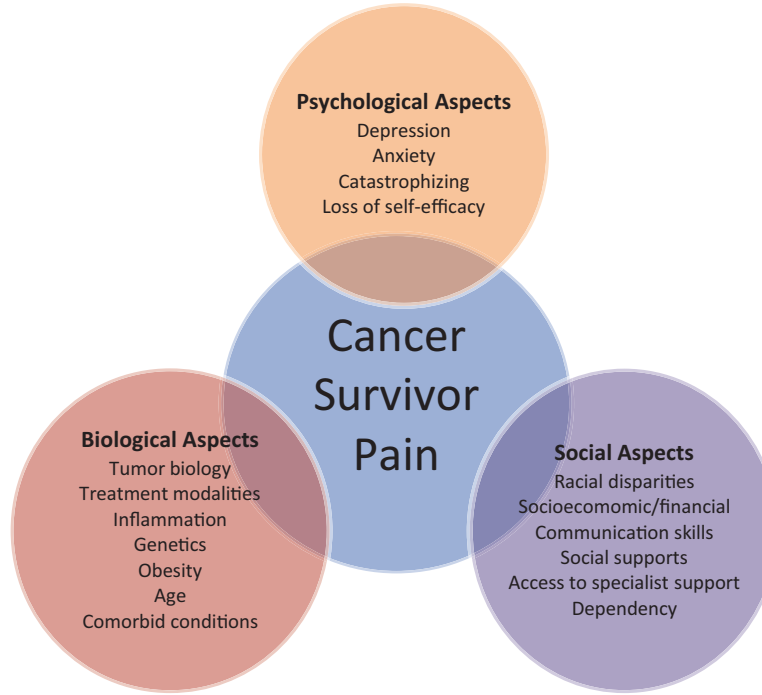

Fig. 10.1 Biopsychosocial factors that contribute to pain in cancer survivors

Strategy in the United States for chronic pain [130]; however, more research is needed [131].

10.6.3 Education and Communication

After completing a pain evaluation and making a tentative pain diagnosis, the provider should educate the patient and family about the diagnosis and goals of care. Formulation with the patient of treatment goals may include consideration of the pain severity, pain interference, pain relief, function, previous pain treatments, meaning of pain, and patient comorbidities. For patients with severe pain, goals may be to make pain bearable, enable mobility and important daily activities, and/or to enable sleep. Depending on the outcome of the discussion, the patient and care provider may select sequential trials of treatments, progressing from non-pharmacologic to pharmacologic approaches.

In general, educating patients about pain and engaging them in pain self-management are other important components of the National Pain Strategy. Goals of education include increasing patient self -efficacy, motivation, and adherence [132]. Pain education can reduce pain in cancer patients and is an area of active research [133]. Helpful physician skills include empathic communication, open-ended questions, coaching, and identifying and addressing patient's specific needs and concerns and barriers [134]. Patient education should be tailored to individual needs, enable patients and caregivers, and include assessment of social and cultural barriers. Communication with family and other healthcare providers who may be involved may contribute to a more complete understanding of the clinical issues related to pain control and enhance care coordination [135].

10.6.4 Multidisciplinary/ Interprofessional Management

Depending on the patient's needs and locally available resources, the care provider ideally may assemble a multidisciplinary team or develop a

cadre of referral sources. The potential roles of members of this team are described below. Many of these providers can offer non-pharmacologic interventions.

Nursing professionals are uniquely positioned on the front lines of most healthcare settings and specialties to be the first clinician assessing a patient's symptoms. Therefore, nurses throughout primary, secondary, and tertiary care settings have the opportunity to identify pain syndromes earlier and provide support and solutions to restore cancer survivors to optimal functional levels [136]. Nurses overcome factors that contribute to underreporting and undertreatment of pain in cancer survivors. They can also facilitate the care of cancer survivors and their families by assisting in coordination and communication between patients, oncologists, primary care providers, and other healthcare professionals to promote improved quality of life and function [137]. Nurses provide compassion and increase therapeutic effectiveness of pain relief interventions by bearing witness through skills including but not limited to unfettered observation, deep listening, and constructive feedback [138]. Advance practice nurses may perform initial evaluations and manage pain.

Specialists in physical and rehabilitation medicine may be considered where there are problems with pain, mobility, or function. Evidence is increasing for the physical medicine interventions in postsurgical and postradiation pain syndromes characterized by stiffness, decreased function, and pain (presented elsewhere in this chapter). Patients with myofascial syndromes and bone pain may also benefit from physical medicine assessment. Overcoming these barriers may help with increasing physical activity in the long term for survivors, as well as finding employment [139].

Psychologists may be helpful for patients expressing distress about pain or distress in general. Evidence is increasing that psychological and psychosocial interventions have modest size effects in patients with cancer pain [140] and for cancer survivors with pain [141, 142]. Specific psychological conditions that may affect the success of pain management include catastrophizing [143], lack of self- efficacy, and cancer-related PTSD [144]. Pain catastrophizing is addressed with cognitive behavioral therapy. Self-efficacy is a sense of confidence in dealing with specific situations and may be important in reducing distress and improving quality of life [145–147]. Self-efficacy of the caregivers can also contribute to better communication and management of pain at home. Hypnosis is the application of mental imaging approaches for pain relief and can be effective in different pain syndromes [148, 149].

Social workers can provide psychoeducation and crisis intervention, assess patient's and family members' strengths and competencies to help restore a sense of control and direction, and explore perceptions of symptoms from the patient's and family's perspectives [150]. Social workers assess the "patient within their environment", which includes the family, cultural, social and interpersonal aspects of pain and other symptoms. They may also assist patients to find social support networks and other resources for needed services; reimbursement may not routinely be available for psychosocial and other approaches to managing pain.

Pain physicians can be helpful in patients with multiple pain problems, intractable pain, or where multiple medications and approaches are necessary. Interventional specialists can be helpful in determining which patients might benefit from procedures such as dorsal column stimulation, epidural analgesia, and kyphoplasty.

Integrative therapy includes a wide range of approaches, including massage, aromatherapy, imagery, complementary medical approaches, and mind-body interventions [151]. There is an emerging body of evidence that some integrative approaches, such as mind-body approaches [152, 153] and acupuncture [154], can reduce symptoms in cancer survivors, especially fatigue.

10.7 Guidelines

Recently, guidelines for pain evaluation and management in cancer survivors have been published and provide helpful recommendations and are

summarized below. Until there is a strong evidence base for cancer survivor specific pain evaluation and management, these guidelines provide helpful recommendations.

10.7.1 The National Comprehensive Cancer Network (NCCN)

The NCCN Survivorship Panel provides recommendations for the management of eight categories of cancer pain syndromes, neuropathic pain, chronic postoperative pain, myalgias/arthralgias, skeletal pain, myofascial pain, gastrointestinal/urinary/pelvic pain, lymphedema, and postradiation pain, in a convenient flowchart format, accompanied by a concise discussion [155].

10.7.2 American Society of Clinical Oncology (ASCO)

The ASCO guidelines provide a set of principles, a comprehensive evidence review and assessment of complexities in managing chronic pain in cancer survivors, and discussion of the risks and benefits of opioid therapy [156]. The guideline critically reviews available information with evidence-level rankings, and the discussion stresses that pain in cancer survivors is a new area and the need for a better evidence base for all aspects of pain in cancer survivors. The recommendations are summarized in Table 10.6.

10.8 Pharmacological Management

Treatment options are usually derived from what is known about pain syndromes in non-cancer patients or in patients with advanced cancer. Treatments do work in some patients, but at this time for the most part, we cannot predict which treatment will be successful for a given patient. With individual variability among patients, sequential trials are reasonable. Participation in clinical trials, if available, should be encouraged.

10.8.1 Adjuvant Analgesics

Adjuvant analgesics are non-opioid medications that provide analgesia and include acetaminophen and nonsteroidal anti-inflammatory agents (NSAIDs) which may be helpful for treating musculoskeletal pain. Additional agents include tricyclic antidepressants, gabapentinoids, antiepileptic drugs, and serotonin-norepinephrine reuptake inhibitors that may alleviate neuropathic pain and calcitonin for bone pain. Topical analgesics include topical NSAIDs, capsaicin, and lidocaine preparations [157, 158].

10.8.2 Opioids

While opioids are the first-line treatment for patients with moderate to severe cancer pain, their use in long-term pain management of chronic pain is questioned because of the lack of long-term data and concerns about side effects and diversion. In response to increasing opioid death rates from opioid overdoses, the Centers for Disease Control guidelines were written for patients with chronic pain who do not have ongoing active cancer or are receiving palliative care management [159]. The American Society of Clinical Oncology has presented a policy statement on protecting access to opioids for patients with cancer-related pain. The policy reviews current safe prescribing practices, the importance of more research to provide a better evidence base, and access to pain medications for patients with pain [160]. In a retrospective case-control cohort study of cancer survivors more than 5 years after diagnosis, opioid prescription rates for cancer patients aged 18–64 Yrs were greater than the general population, with an OR of 1.22 (95% CI 1.11–1.34), including at 10 years after diagnosis. As this was a pharmacy database analysis, no information on pain diagnoses or epidemiology was available [161].

Risk management and safe prescribing are thoroughly reviewed in the ASCO guidelines. Further information on risk assessment related to using opioids includes evaluating for medical conditions such as sleep-disordered breathing, mental conditions, chemical coping, risk stratification, assessment for drug-related behaviors and aberrant behaviors, plans for response to aberrant behaviors, and communication and documentation [162].

Where a decision is made that opioids should be prescribed, it is critical that providers document pain assessments, pain diagnoses/syndromes, pain relief, effect of analgesics on function and mood (and constipation), and the prescriptions written on that encounter.

10.8.3 Cannabis

There is great interest in cannabinoids for pain management. However, the evidence to date is weak, and no recommendations can be made [163, 164]. Physicians should follow relevant regulations regarding the use of cannabis, which at this time of writing was legal in 29 states and the District of Columbia and was illegal at the Federal level [165].

10.9 Pain Management: Pathophysiologic Categories

10.9.1 Neuropathic Pain

In a recent systematic review of treatments for neuropathic pain in general, first-line treatment recommendations were made for tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin; second line for lidocaine patches, capsaicin high-concentration patches, and tramadol; and third line for strong opioids and botulinum toxin A [166]. In a systematic review of medications for cancer neuropathic pain, opioids provided pain relief in 95% of patients [167]. Topical preparations of lidocaine, such as the lidocaine 5% patch, have also been effective in patients with peripheral neuropathy and postherpetic neuralgia [157].

10.9.2 Musculoskeletal Pain

Treatment of musculoskeletal pain is interdisciplinary, including exercise, massage, and NSAIDs, and can include invasive procedures such as radiofrequency denervation and steroid injections. For patients with spinal stenosis, epidural steroid injections can provide significant relief. Persistent pain from vertebral body collapse is another significant problem. One study reports patients with skeletal-related events from prostate cancer were reported to require more opioid analgesics for more than 6 months after the event [168]. Evidence supports kyphoplasty for patients with vertebral bone collapse [169], and whether a patient may benefit from this intervention should be discussed with a physician who does these procedures. Muscle pain does not respond well to opioids but improves with physical therapy, therapeutic exercise, muscle relaxants, antispastic agents, and injections into the trigger points [170, 171].

10.10 Pain Management: Surgical Pain Syndromes

10.10.1 Postsurgical Pain

There have been few randomized clinical treatment trials. In one trial, 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 [172]. Emphasis has been placed on preventive measures such as perioperative gabapentin, surgical technique, and minimizing the severity of postoperative pain [173]. Many patients pursue non-pharmacologic

Table 10.2 Common surgery-related pain syndromes

Syndrome	Cancer	Comments	Management approaches
Amputation	Extremity sarcoma	Pain in stump	Prosthetic fit
		Phantom pain	Analgesics
		Interference with function	Physical therapy
Radical neck dissection	Head and neck cancer	Pain can be felt in the neck, shoulder, and arm	Physical therapy Analgesics Acupuncture
Postmastectomy pain	Breast cancer	Pain felt in the breast followed by the axilla, arm, shoulder, fingers/ feet, and neck [50]	Analgesics – amitriptyline, venlafaxine, topical analgesics Physical therapy and rehabilitation
		May report shooting, aching, and burning pain and demonstrate allodynia	
		Limited use of the arm	Physical therapy and rehabilitation
Post-thoracotomy pain	Lung cancer	Shooting or burning pain can be exacerbated by movement	Analgesics
Lymphedema	Breast cancer	Upper extremity	Multimodal/complete decongestive therapy
	GYN cancer, GU, pelvic malignancies	Lower extremity	Multimodal/complete decongestive therapy

Adapted from Sect. 10.4.1

Table 10.3 Common radiation-related pain syndromes

Syndrome	Description	Management approaches
Cervical dystonia	Head and neck patients	Physical therapy
Brachial plexopathy	Pain and weakness in the arm and shoulder that may progress	Analgesics
Radiation enteritis	Diarrhea	Gastrointestinal workup
	Pain may be experienced in abdominal, back, rectal, perianal, and anal areas	
Pelvic syndrome	Lower abdominal pain	Analgesics
	Dyspareunia	Topical lidocaine
	Lower extremity lymphedema	Decongestive therapy
	Pelvic insufficiency fractures	Rest, analgesics
Lumbosacral plexopathy	Pelvic and leg pain, sometimes with weakness	Analgesics

Adapted from Sect. 10.4.2

measures for pain relief; however, trials of analgesics and multimodality therapy may also be necessary to control postsurgical pain syndromes (Tables 10.2, 10.3, 10.4, and 10.5).

10.10.2 Phantom Pain

Data are limited on the appropriate management of patients with phantom pain. A large variety of treatments have been studied in small numbers of patients with few findings [175]. Phantom pain has both peripheral and central nervous system components. There has been much interest in nonmedical approaches such as transcutaneous electrical nerve stimulation (TENS), hypnosis, and acupuncture with limited data. The use of mirrors can induce analgesia in the phantom limb [176]. Regarding pharmacologic treatments, small randomized clinical trials have found analgesic effects for morphine 70 mg to 200 mg orally [177] and gabapentin for up to 2400 mg daily at 6 weeks [178]. A small crossover trial found that dextromethorphan 60 or 90 mg orally twice a day decreased pain intensity by greater than 50% [179]. Ketamine boluses increased pressure pain thresholds and reduced windup pain [180]. A randomized trial of amitriptyline up to 125 mg daily did not show any effect [181]. Other approaches include anecdotal evidence for the SNRI inhibitor milnacipran [182]. The overall effectiveness of pharmacologic interventions was considered unclear in a

Table 10.4 Common chemotherapy-related pain syndromes

Syndrome		Cancer primary sites	Description	Management
Chemotherapy-induced peripheral neuropathy			Numbness and tingling in hands and feet	ASCO statement [219]
	Vincristine	Acute leukemia, lymphoma	Sensory, motor, and autonomic neuropathy	
	Oxaliplatin	GI	Cold sensitivity in the hands, feet, and upper airway	
	Bortezomib	Myeloma		
	Imids (thalidomide)	Myeloma		
	Taxanes	Head neck, breast, ovary		
Steroids		Hematologic malignancies	Osteonecrosis	
			Shingles	Adjuvant and topical analgesics
Hormonal therapy	Aromatase inhibitors/ estrogen deprivation	Breast cancer	Arthalgias and painful stiffness	Physical therapy
			Osteopenia/fractures	Monitoring
			Atrophic vaginitis	
			Dyspareunia	Topical lidocaine
	Androgen deprivation	Prostate cancer	Osteopenia/fractures	Monitoring
Bisphosphonates, denosumab			Osteonecrosis of jaw	

Adapted from Sect. 10.4.3

Table 10.5 Bone marrow transplantation chronic graft versus host disease-related pain syndromes

Site	Painful manifestation	Comments
Skin	Ulcerations, fibrosis	No specific guidelines for pain management
Eyes	Dry gritty eyes	Topical NSAID, serum containing eye drops [176]
Mouth	Ulcers, dry mouth	No specific guidelines for pain management
Mucosal surfaces	Vagina, glans penis	No specific guidelines for pain management

Adapted from Sect. 10.4.5

recent Cochrane review [183], and the best evidence pertains to perioperative management of phantom pain [184].

10.10.3 Post-radical Neck Dissection Pain

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 [185]. Randomized clinical trials of exercise [186, 187] and acupuncture [188, 189] have reported decreased pain, and these interventions merit further study.

10.10.4 Postmastectomy Pain Syndrome

There have been few trials related to treatment of PMPS [190]. Amitriptyline in a dose range of 20 to 100 mg was found to be effective in a small randomized crossover trial [191]. 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 [192]. Topical capsaicin at strength of 0.025% has been effective in small single-arm trials [193, 194].

Table 10.6 ASCO guidelines chronic pain in cancer survivors (abbreviated summary)

1. Screening and assessment
1.1 Screen for pain at every encounter
1.2 Conduct a comprehensive initial pain assessment
1.3 Be aware of cancer-related pain syndromes and treatments
1.4 Consider the differential diagnosis of new onset pain
2. Treatment and care options
2.1 Enhance comfort, improve function, limit adverse events, and ensure safety in the management of pain
2.2 Engage patients, family, and caregivers
2.3 Determine the need for other professionals and their roles
2.4 Consider non-pharmacologic interventions
2.5 Consider pharmacologic interventions – miscellaneous analgesics
2.6 May prescribe topical analgesics
2.7 Long-term steroids not recommended for pain control
2.8 Assess risks of pharmacologic approaches
2.9 Follow local regulations regarding cannabis products
2.10 May prescribe a trial of opioids in carefully selected patients, and add non-opioid analgesics as clinically indicated
3. Opioids
3.1 Assess risks and benefits of long-term opioid therapy
3.2 Understand terminology regarding opioid use
3.3 Incorporate a universal precautions approach in opioid prescribing
3.4 Understand laws and regulations pertaining to controlled substances
3.5 Educate the patient and family about long-term risks and benefits of opioid use with attention to storage and disposal and myths about opioids
3.6 Taper opioids when opioids are no longer needed

10.10.5 Post-thoracotomy Pain Syndrome

Earlier reviews found little evidence for effective interventions [195]. Capsaicin was effective in a trial for surgical neuropathic pain (described above) [172], and topiramate was active in a small series of patients [196]. This remains a difficult problem [197]. One group compared transdermal nitroglycerin to transdermal nitroglycerin 5 mg/day with etodolac in an open label trial in patients with etodolac insensitive pain. An improvement in VAS pain severity, breakthrough pain, and sleep efficiency was observed on day 14 of treatment [198].

10.10.6 Lymphedema

Current recommendations for management include complete decongestive therapy, a multimodal approach that includes multilayer compression bandages, manual drainage, gentle exercise, and meticulous skin care [199]. Lymphedema patients have unmet educational and symptom management needs [64]. Analysis of responses by 802 persons with primary lymphedema found an association between self-care practices such as the use of compression garments and exercise and being less likely to report pain [200].

10.11 Pain Management: Radiation Pain Syndromes

10.11.1 Neck Syndromes

Physical therapy is the principal intervention to strengthen neck muscle function and posture. Injection of botulinum toxin A can relieve pain from muscle cramps in cervical dystonia, and adjuvant analgesics such duloxetine and gabapentin can control neuropathic pain symptoms [201].

10.11.2 Brachial Plexopathy

Treatment is supportive [202]; symptomatic treatment for pain includes benzodiazepines for paresthesia, tricyclic antidepressants, and antiepileptics, such as carbamazepine [203]. Quality data on treatment is limited. In 1 series of 33 patients, morphine was effective and given long term for 17 patients, and 3 patients improved with chemical sympathectomy [204]. Surgical interventions have generally not been successful [205], although there have been successful case reports of neurolysis and dorsal root entry zone

lesions in patients [206, 207]. A randomized trial of hyperbaric oxygen versus placebo did not show any difference [208]. Non-pharmacological methods, such as occupational therapy, can be helpful for patients [209].

10.11.3 Radiation Enteritis

Radiation enteritis can be treated with diet, endoscopy, surgery, and hyperbaric oxygen [210, 211].

10.11.4 Radiation Pelvic Syndromes/ Pelvic Insufficiency Fractures

Management is usually bed rest and analgesics. Mobilization is necessary to prevent bedsores. Some patients may require hospitalization. Sacroplasty, conceptually similar to kyphoplasty, uses image-guided, percutaneous injection of surgical cement into the fracture [212]. In a multicenter study of patients with pain unresponsive to conventional measures, CT-guided sacroplasty was safe and effective with low complication rates [213]. A single-institution study of 25 patients with cancer-associated sacral insufficiency fractures reported significant pain relief in 80% of patients [214].

10.11.5 Radiation Lumbosacral Plexopathy

If lumbosacral plexopathy results from recurrent cancer, radiation is helpful for pain control.

10.11.6 Osteoradionecrosis

Management options include analgesics, hyperbaric oxygen, antibiotics, and, in a small number of patients, surgical resection of the necrotic bone and reconstruction [215]. A combination of pentoxifylline, tocopherol, and clodronate leads to complete resolution in all patients in a phase II trial [216].

10.12 Pain Management: Chemotherapy

10.12.1 Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Despite many clinical trials, little evidence is available to support pharmacologic approaches for prevention and management of chemotherapy-induced peripheral neuropathy [217]. An ASCO clinical guideline on the basis of available evidence did not recommend any pharmacologic approaches for prevention of chemotherapy-induced peripheral neuropathy and listed 12 medications that should not be routinely offered (acetyl-L carnitine, amifostine, amitriptyline, calcium magnesium for patients receiving oxaliplatin therapy, diethyldithiocarbamate (DDTC),

Table 10.7 ASCO Chemotherapy-induced peripheral neuropathy guidelines [220]

For treatment of CIPN, clinicians may offer	In the absence or alternate options for CIPN, clinicians may offer the following based on data supporting their efficacy in other neuropathic conditions[a]
Duloxetine • 60 mg daily. May start at 20–30 mg daily and increase to 60 mg after 1 week as tolerated • Moderate recommendation	Gabapentin • Start at doses of 100–300 mg/day, and titrate up to 1200 to 3600 mg/day in three divided doses [166] • Adjust dose for renal dysfunction
	Tricyclic antidepressants • Nortriptyline – start at 10 to 20 mg bedtime and may titrate every 3–5 days by 10 mg/day, max of 160 mg/day [221] • Desipramine – start at 12.5–25 mg qhs and may increase by 25 mg/day every 3–7 days, max of 150 mg/day [222]
	Compounded gel • Baclofen (10 mg) + amitriptyline (40 mg) + ketamine (20 mg)

[a]Adapted from Ref. [220]. Doses are based on recommendations for nonmalignant neuropathic pain syndromes

glutathione for patients receiving paclitaxel/carboplatin therapy, nimodipine, Org 2766, all-trans retinoic acid, rhuLIF, Vitamin E, and venlafaxine). The use of duloxetine, a serotonin-norepinephrine reuptake inhibitor, as a treatment, is supported by one multicenter RCT involving 231 patients. Patients were randomized to either duloxetine 30 mg daily × 1 week followed by 60 mg daily × 4 weeks versus placebo. Results showed improved reports of numbness and tingling in the feet but not the hands of patients in the treatment arm [218].

The ASCO guidelines recommend a trial of duloxetine for treatment of chemotherapy-induced peripheral neuropathy. The guidelines suggest gabapentinoids, topical analgesics, and tricyclic antidepressants as additional pharmacologic options [219] (see Table 10.7 CIPN guidelines). More research and high-quality studies are needed.

10.13 Pain Management; Hormonal Therapy

10.13.1 Aromatase Inhibitor (AI) Musculoskeletal Syndrome

Treatment approaches include a drug holiday, switching to other aromatase inhibitors [223] or to tamoxifen, and a trial of NSAIDs. A recent meta-analysis identified pharmacologic measures (trial of methylprednisolone, switch of AI inhibitors, trial of thymosin-1, and duloxetine) and acupuncture as having a moderate effect on AI-related pain [224]. One randomized controlled trial supports exercise for the reduction of AI-related symptoms. In the Hormones and Physical Exercise trial, 121 postmenopausal women with AI-related arthralgias for more than 6 months were assigned to receive either a supervised exercise regimen which included 150 min of aerobic and resistance training to total 150 min/week versus usual care. The treatment arm experienced a significant reduction in pain severity, increased weight loss, and improved exercise capacity [225].

10.13.2 Atrophic Vaginitis/ Dyspareunia

Interventions for management include lifestyle changes such as smoking cessation, regular coitus/other sexual activities to improve blood flow and vaginal pH, vaginal penetration with lubricated fingers or dilators to prevent fibrotic changes and stretch tightened vaginal walls, stress management to reduce fear of painful intercourse, and avoidance of feminine hygiene products that may reduce normal vaginal flora. If lifestyle changes are not sufficient to reduce symptoms, nonhormonal therapies include vaginal moisturizers, oils, pH-balanced gel, and lubricants, although these cannot reverse vaginal atrophy once it occurs [107]. A recent approach to dyspareunia centers on the finding of increased nerve proliferation in the vaginal vestibule during estrogen deprivation. In a small randomized trial, application of lidocaine to the vaginal vestibule significantly reduced penetrative pain [226].

10.14 Pain Management: Stem Cell Transplantation

Guidelines have been published for management of cutaneous and musculoskeletal manifestations of chronic GVHD [227], but no specific guidelines for related pain management exist. For patients with dry eyes from ocular GVHD, autologous serum eye drops and topical NSAIDs may provide relief [174].

10.15 Pain Management: Medication-Related Osteonecrosis of Jaws

For patients who are symptomatic but have no physical findings, antibiotics and analgesics are indicated. When there is exposed bone but no pain, antibacterial rinses and regular follow-up every 3 months are needed. Where there is infection, pain, or erythema, then surgical debridement or resection may be indicated [115, 228].

10.16 Future Directions

Determinants of which cancer survivors develop treatment-related pain syndromes are complex and often involve aspects of the patient (psychological aspects, genetics of inflammatory response and drug metabolism, age, sex, social aspects – social support, race, income, educational level) and treatment modality. This highlights the need for provider and patient education and the potential utility of a biopsychosocial approach to long-term management of pain. The identification of high-risk patients will open the way to study preventive measures and consider pain as a late and long-term effect. Similarly, attempts to redefine syndromes more precisely for postmastectomy pain [229], postsurgical pain [230], and CIPN [231] will lead to better case finding criteria and phenotyping for further study.

An important direction may lie in improved cancer survivorship transition. Cancer survivors are generally not prepared for pain as a long-term component of survivorship. Better education, communication [232, 233], and preparation for pain and other symptoms as part of the survivor transition [234] may enhance adherence and more of a partnership with the healthcare team to managing pain. For example, improved efforts to explain pain as a multidimensional problem and illustrate how lifestyle factors and psychosocial circumstances can affect pain and vice versa may enable our patients to be more open to various approaches to manage pain. This brief intervention from a physician or nurse may better prepare survivors to employ a number of approaches that may help decrease the impact of pain experienced over time.

The profound lack of good quality clinical trial data to guide management of pain syndromes in cancer survivors is a significant challenge for cancer survivors experiencing pain. There is a major need for more basic research to understand mechanisms and develop new treatments and for clinical trials to determine which treatment approaches are best for various pain syndromes. These steps are essential for developing high-quality effective pain control approaches in cancer survivors. This requires funding and participation in clinical trials by cancer survivors. Because there are many psychosocial challenges among cancer survivors, particularly survivors with persistent pain, this represents an opportunity to further examine the value of psychosocial interventions including pain education and communication. Additional research on how to deliver multimodal pain interventions is needed. For the field of musculoskeletal pain, the Department of Veteran Affairs has recently sponsored a state of the art conference comparing models of care [235]. At the healthcare system level, the ability of the patient to get reimbursed for multimodal pain management remains an important barrier.

Pain can prove to be a major adversary for the cancer survivor. Pain in survivors is an area that has progressed from an initial focus on side effects of surgery to include evaluation of preexisting pain disorders and pain associated with comorbid health conditions. The increased emphasis on pain in cancer survivorship in research and in healthcare practice should improve the quality of care received by cancer survivors and ideally their long-term function and well-being.

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Part IV

Problem Area: Function

Cognitive Dysfunction

11

Robert J. Ferguson, Catherine M. Bender, Brenna C. McDonald, James C. Root, and Shelly Kucherer

11.1 Introduction

Cognitive change that results from various forms of cancer and treatment has gained growing research attention since publication of the first edition of the *Handbook of Cancer Survivorship* in 2007. A brief literature search on MEDLINE using the search terms "cancer," "cognitive change," "cognitive dysfunction" and "cognitive impairment" resulted in growth from 180 publications in 2007, to 321 in 2012, and 793 published in 2016. The history of clinical research on cancer-related cognitive dysfunction (CRCD) largely began with evaluation of cancer of the central nervous system (CNS) but expanded greatly in the early 1990s to include study of the cognitive effects of non-CNS tumors and systemic therapies. In addition, over the time span since the *Handbook's* first edition, research has been completed on various non-pharmacological and pharmacological treatments of CRCD. This chapter will summarize CRCD research related to non-CNS and CNS cancer, the emerging treatment approaches, and future directions for research.

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11.2 Cognitive Dysfunction Associated with Non-CNS Disease

11.2.1 Background and Prevalence

The most widely studied population with non-CNS CRCD is early stage breast cancer [1, 2] but a number of studies have also included patients with lymphoma [1, 3] spanning the course of about two and a half decades. Most investigations in that period focused on memory problems associated with late cognitive effects of chemotherapy (e.g., [4]) or endocrine therapies [5] among breast cancer survivors (BCS). While the exact prevalence is unknown, 25–75% of chemotherapy recipients are estimated to demonstrate

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evidence of CRCD [2]. The wide variation in estimates likely has much to do with differences in research methods, including the definition of cognitive decline used, timing of assessment of cancer survivors (e.g., during active treatment, acute recovery, or post-treatment phases), neurocognitive tests used in different studies, variations in research design (e.g., cross-sectional and longitudinal studies), and variations in cancer populations studied [2]. Standards of neuropsychological testing composite scores and other methodological conventions have been proposed to help clarify between study comparisons [6, 7]. Regardless, if we assume 50% of chemotherapy recipients (median of the 25–75% prevalence range noted above) experience CRCD, the public health impact on survivor function and quality of life is formidable; especially in light of growing numbers in the cancer survivor population (currently 15.5 million) [8].

11.2.2 Research on Non-CNS CRCD

Research on the cognitive effects of chemotherapy dates back to the early 1980s with small samples of individuals with cancer, but no control groups or controls for effects of emotional distress (e.g., depressive symptoms) on neuropsychological test performance were utilized. In addition, many of the patients in such early work were evaluated soon after the completion of chemotherapy, when the acute effects of various treatment exposures were expected to depress neurocognitive performance [9]. In an improved design, Wieneke and Dienst [10] evaluated 28 breast cancer chemotherapy recipients 6 months post-treatment. Seventy-five percent scored >2 standard deviations below published norms on one or more neurocognitive measures and outcomes were found to be unrelated to depression, type of chemotherapy, or time since treatment. In a larger cross-sectional study, Ahles et al. [4] compared long-term breast cancer and lymphoma survivors (>5 years post-treatment) who completed chemotherapy ($N = 71$) or local therapy ($N = 57$). In order to control for demographic and neurobehavioral risk factors, the two survivor groups were matched on age, education, and IQ, and were excluded if they had a history of neurologic disorders, substance abuse, or severe psychiatric illness. Thirty-nine percent of chemotherapy recipients compared to 14% of local therapy patients demonstrated neurocognitive dysfunction ($p < 0.002$).

With a lack of pre-treatment assessments, a number of longitudinal studies evaluating patients undergoing cancer treatment were then conducted. These studies compared matched, same-cancer controls not undergoing systemic therapy with chemotherapy recipients and a healthy control group. Overall, the longitudinal studies completed over the last two decades have been consistent with early research. A subset of survivors who receive adjuvant chemotherapy have detectable neurocognitive declines in verbal memory, verbal working memory, and processing speed [2]. The neurocognitive declines are generally mild to moderate, and have been found independent of emotional distress or other neurobehavioral factors [2, 6, 11–13]. In addition, studies have found poorer than expected cognitive performance in breast cancer patients prior to chemotherapy and in those not receiving chemotherapy [14–20]. These findings suggest a role for patient-related risk factors (e.g., age, cognitive reserve, fatigue) [21, 22] and/or the cancer disease process itself in cognitive decline in this population. In addition, research has suggested cognitive effects of cancer treatments other than chemotherapy, including surgery, general anesthesia, local radiation, and endocrine therapies [23–25]. Ovarian and testicular cancer survivors have also been studied since 2010, with similar findings in terms of negative cognitive effects of chemotherapy and endocrine treatments in a subgroup of patients [26–29].

11.2.3 Mechanisms

An active area of research is the investigation of potential biological mechanisms of CRCD. Ahles and Saykin [30] proposed a number of candidate mechanisms for chemotherapy-related cognitive changes, as well as for potential common risk

factors for the development of cancer and cognitive problems. These include direct neurotoxic effects related to the passage of chemotherapy agents across the blood-brain barrier; chemotherapy-induced DNA damage caused either directly by chemotherapy agents or via increased oxidative stress, or chemotherapy-induced telomeric shortening leading to accelerated cell aging; and cytokine dysregulation and inflammation. All of these events could lead to increased oxidative stress and a cycle of further increased DNA damage and additional cytokine release. Variability in genes related to neural repair and/or plasticity or neurotransmission can also increase individual susceptibility to cognitive changes. Changes in brain activation and cognitive function have also been found to be related to chemotherapy-induced amenorrhea and hormone dysregulation [31] and oxidative DNA damage [32].

11.2.4 Genetic Influences

Genetic variability can influence each of the above factors, potentially explaining why a subgroup of patients is more likely to experience CRCD. For example, variation in genes related to blood-brain transporters may influence the amount of chemotherapy crossing the blood-brain barrier for a given patient [33–42]. Studies examining genetic factors have suggested a role for APOE [3, 43], COMT [44], and IL1R1 [45] polymorphisms in risk for CRCD. Somatic chromosomal instability has been found to be associated with radiation and chemotherapy treatments, as well as with perceived stress levels in breast cancer patients [46].

11.2.5 Chemotherapy Agents

As reviewed by Seigers et al. [47, 48], preclinical in vivo studies have investigated the effect of various chemotherapy agents and other biologics (e.g., antimetabolites, DNA cross-linking agents, mitotic inhibitors, anti-hormonal agents, and molecular-targeted agents) on adverse neurological function, including cognitive deficits. Specific chemotherapy agents have been studied with regard to apoptosis, blood supply, cerebrospinal fluid composition, electrophysiology, histone acetylation, inflammation, brain morphology, neurogenesis/gliogenesis, neurotransmitter/monamine release, and oxidative stress, with findings often demonstrating that different agents may show similar overall effects in these domains, suggesting that common indirect mechanisms may lead to CRCD [48].

11.2.6 Inflammation

Changes in pro-inflammatory cytokine levels may also accelerate cognitive decline in patients with cancer [49–51]. Clinical studies have examined levels of various cytokines before, during, and after chemotherapy treatment, and found that cytokine levels and association with objective and subjective cognitive function vary over the course of treatment [16, 17, 52–56]. Patel et al. found that higher sTNF-RII levels were associated with poorer memory before surgery and adjuvant therapy in women with breast cancer [17]. This suggests cancer itself can trigger processes leading to cognitive dysfunction. In contrast, higher levels of IL-6 and TNFα were related to more self-reported cognitive complaints in women during chemotherapy for breast cancer [51, 54].

In addition, higher TNFα levels were related to poorer verbal memory and lower left hippocampal volume in 42 women with breast cancer 5 years post-chemotherapy [57], suggesting that an inflammatory response may be triggered by the introduction of chemotherapy and maintained well after completion of systemic treatment. Different chemotherapy regimens have also been shown to differentially affect cytokine levels and downstream effects on survivor function [51]. For example, increases in inflammatory cytokines are associated with symptoms commonly experienced by individuals with cancer, including depressive symptoms, anxiety, fatigue and sleep problems, also referred to as "sickness behavior." These symptoms commonly co-occur with cognitive complaints [58–61]. Moreover,

medications used to manage these symptoms and the presence of comorbidities may influence CRCD [62]. More research is needed on identifying specific CRCD pathways, including identifying which agents cause which types of cytokine release and the downstream effects on survivor cognitive function and quality of life.

11.2.7 Endocrine Influences

Changes in reproductive hormones such as estrogen with cancer and cancer therapy may also be associated with CRCD. Estrogen exposure enhances learning and memory and influences brain areas that are rich in estrogen receptors and support these cognitive functions. Estradiol (E2) influences neuronal growth and synaptic plasticity, and has anti-inflammatory properties including inhibition of pro-inflammatory cytokines (IL-6, IL-8, TNF) [63]. Decreasing E2 levels over the course of a woman's lifespan are associated with cognitive decline [64, 65], and this may be exaggerated in women with breast cancer. During and after breast cancer therapy, E2 levels are significantly lower in postmenopausal women. Treatment with aromatase inhibitors is associated with aromatase inhibition of nearly 98%, resulting in significant suppression of plasma E2 levels after 15 weeks of aromatase inhibitor therapy [66]. Ovariectomized mice have significant hippocampal spine synapse loss with 4 weeks of exposure to the aromatase inhibitor letrozole [67]. Poorer cognitive function has been associated with aromatase inhibitor therapy in postmenopausal women with early stage breast cancer [68]. More research is needed to determine the precise role of reduction in estrogen and other hormones (e.g., androgen suppression therapy in prostate cancer) in CRCD.

11.2.8 Summary of Mechanisms

The mechanisms involved in non-CNS CRCD are multiple and likely have independent as well as interacting influences on cognition and quality of life. Much of the research cited here has sought to isolate the influence of cancer treatment or other factors (such as inflammation) on cognitive performance, and thus has controlled for the influence of emotional distress through excluding cancer survivors with high emotional distress. However, in clinical settings, many survivors may present with longstanding anxiety or mood disorders or acute episodes of emotional adjustment difficulty at some point in their cancer experience. It may be that chronic emotional distress leads to CNS vulnerability to late cognitive effects of non-CNS cancer or cancer therapy. Or, acute distress, concurrent with cancer, may exacerbate existing CRCD [69]. In summary, the multiple mechanisms involved in non-CNS CRCD may have direct, interacting or perhaps even reciprocal influences on cognitive function (Fig. 11.1).

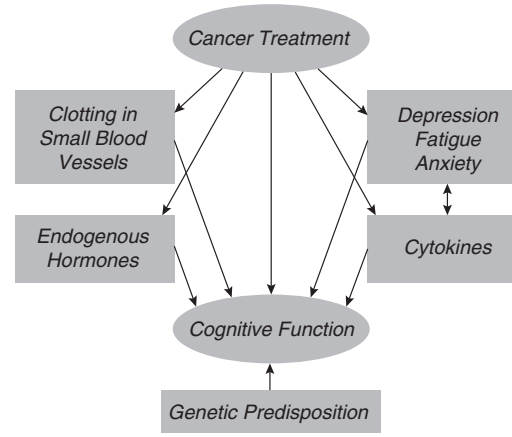

Fig. 11.1 Multiple influences on cognitive function. (Reprinted with permission, Ref. [70])

11.2.9 Neuroimaging Studies

Over the past 10 years, an increasing number of structural and functional neuroimaging studies have examined the neural substrate of CRCD using MRI or PET (for reviews and commentary, see [71–77]). Functional neuroimaging approaches have most commonly used measures of executive function and working and episodic memory, given the cognitive alterations commonly shown in these domains in cancer patients. Retrospective studies of BCS cohorts and case

studies have found alterations in task-related brain activation [32, 78–85] and resting cerebral metabolism [83] in patients who had received chemotherapy relative to those who did not. Reduced gray matter volume has also been demonstrated in chemotherapy-treated BCS using voxel-based morphometric (VBM) analyses [32, 86–88] and other volumetric techniques [55, 89]. In addition, decreased white matter integrity has been shown using diffusion tensor imaging (DTI) [86, 88, 90–92].

In subsequent prospective and longitudinal work, structural MRI and DTI studies have demonstrated significant reductions in gray matter volume/density [93–96] and white matter integrity [97] that appear specifically attributable to breast cancer chemotherapy, though some differences have also been shown prior to systemic treatment [93, 94, 96–98]. Prospective longitudinal studies have also shown alterations in brain activation in breast cancer patients relative to controls prior to systemic treatment, and examined the relationship of activation to variables such as fatigue, worry, mood, and anxiety [22, 99–102]. Increased working memory-related functional MRI (fMRI) activation relative to controls after surgery but prior to breast cancer chemotherapy has been found in multiple studies [103–105], though relative between-group differences in activation at times depend on analytic approach and covariates selected [102, 105, 106].

Reduced task-related activation has also been observed in the near-term (i.e., 1–6 months) after breast cancer chemotherapy, with at least partial recovery over time [104, 107]. A similar pattern of decline with partial recovery has been shown for regional grey matter volume/density [94, 95] among BCS. This pattern of longitudinal change is consistent with the overall cognitive findings of greatest cognitive decline during and shortly after chemotherapy, with significant recovery over time, though persistent deficits may remain for a subgroup of cancer survivors. Which patients are at greatest risk remains the subject of considerable research. As noted above, greater age at diagnosis, lower cognitive reserve, and genetic vulnerability may increase risk for cognitive declines after chemotherapy.

Alternative patterns of activation change over time have also been demonstrated, and may be dependent on cognitive domain assessed and treatment type or dose (e.g., patients treated with chemotherapy versus those who are not, conventional-dose versus high-dose chemotherapy, anthracycline- versus non-anthracycline-based regimens) [84, 108–110]. Several studies have also demonstrated direct correlations between brain structure/function and subjective or objective cognitive performance or peripheral neuropathy symptoms in BCS [32, 55, 57, 82, 83, 90, 91, 94, 96, 97, 99, 105, 107, 111, 112] as well as between brain metrics and biological variables such as cytokine levels and menopausal status [31, 55, 93, 113].

A small number of studies have also found alterations in brain metabolites after breast cancer chemotherapy using magnetic resonance spectroscopy [57, 86, 88]. Pulsed arterial spin labeling (PASL) MRI has demonstrated alterations in cerebral blood flow specific to chemotherapy-treated patients which are both related to and independent of gray matter changes, and which correlate with neuropsychological performance and symptoms related to peripheral neuropathy [112, 114]. A variety of self-report and objective cognitive assessment tools have been shown to correlate with neuroimaging findings, including measures of attention, memory, and executive function. Some studies have demonstrated correlations with specific tests, while others have utilized cognitive domain scores.

Over the past 5 years, studies have implemented network and connectivity analyses utilizing structural MRI and task-based and resting-state functional MRI data. This work has demonstrated alterations in connectivity metrics in breast cancer patients who received chemotherapy relative to those who did not and healthy controls; such changes have also been shown to relate to cognitive function, further elucidating the mechanisms for these impairments [108, 115–124]. Most recently, structural and functional network alterations have been demonstrated in breast cancer patients prior to any treatment, including surgery with anesthesia

[125], providing further evidence for a role for cancer pathogenesis in the observed cognitive changes.

Most of the initial neuroimaging work studying CRCD was conducted in breast cancer patients. Studies in other cancer populations, including ovarian, testicular, and lung cancers, mixed solid tumor populations, and stem cell transplant recipients, have shown similar findings, particularly with regard to negative effects of chemotherapy on brain structure and function, but also with regard to cognitive changes in cancer patients prior to systemic treatment [43, 85, 126–131]. Work in prostate cancer has also shown effects of androgen deprivation therapy on brain structure and function, including decreased gray matter volume and reduced brain activation and functional connectivity [132–134].

Overall, cross-sectional and longitudinal structural and functional neuroimaging studies have detected alterations in brain gray matter, white matter, blood flow, metabolism, activation, and connectivity in cancer populations. The most pronounced effects have been demonstrated within the first several months after chemotherapy treatment, and have been shown to improve over time, though persistent effects have been noted even decades after treatment completion. It is also important to recognize that alterations in neuroimaging metrics have been shown in cancer patients at pre-treatment baseline, and related to aspects of treatment other than chemotherapy. Similar effects have been seen across varying cancer types; the most common findings reported are alterations in brain structure and function in prefrontal and medial temporal regions, consistent with the executive and memory symptoms commonly found in cognitive studies.

11.3 Quality of Life Impact

Quality of life research on the effects of CRCD has generally evaluated occupational and social impacts [13, 135–137]. For example, an online survey of 453 cancer survivors (Tannock and Vardy; www.hurricanevoices.org/today/cognition) demonstrated 62% of survivors reported home problems such as being criticized by family members, avoiding social functions due to embarrassment with memory failures, or having to relinquish responsibilities such as managing home finances. With respect to CRCD work-related problems, survivors have reported being moved to positions of fewer job responsibilities, lower pay, or inability to handle pre-cancer workload. Frustration exhibited by co-workers and supervisors, demotion, and termination have also been reported. BCS with CRCD have been found to have more employment problems, disability, and changes in social and family roles than those without cognitive change [138]. Given the breadth of functional and quality of life disruptions that can arise from CRCD in social and occupational roles, efforts to address CRCD with various forms of intervention have increased since the prior edition of this book.

11.4 Treatment Approaches

Since the 2007 publication of the *Handbook of Cancer Survivorship*, there has been growth in the development and evaluation of non-pharmacological, pharmacological, physical activity, and natural supplement interventions to ameliorate CRCD related to non-CNS disease. Seven reviews of CRCD intervention research have been published from 2014 to 2016, including meta-analyses of limited data [139–145]. The overall conclusion of this literature is that there is some evidence that non-pharmacological approaches offer improvement in cognitive function and quality of life outcomes for cancer survivors.

Small sample sizes, single clinicians delivering treatment, variability in outcome measures used (both self-reported and objective neurocognitive outcomes) and studies completed primarily with BCS limit broad conclusions on efficacy at this point. Pharmacological interventions and studies of natural supplements are limited in number and have mixed results [2, 139, 141]. We briefly summarize non-pharmacological and pharmacological approaches of CRCD and highlight future directions of research.

11.4.1 Non-pharmacological Approaches

The range of non-pharmacological treatments of CRCD has included computer-based approaches, behavioral and educational interventions that teach compensatory strategies, and physical activity/exercise [139, 141, 143]. Computer-based cognitive training is an approach to cognitive rehabilitation that has been examined in BCS and consists of repetitive practice to theoretically foster expanded neural networking around damaged brain regions. Among the benefits of computer-based interventions are that it does not require clinician training and can be accessed by anyone having access to a computer or mobile device. One example of a computer-based CRCD treatment involves an online-administered treatment commercially available from Lumos Labs [146]. In a small (N = 41) RCT, BCS demonstrated improvement over wait-list controls on the Wisconsin Card Sorting Test (p = 0.008), Delis-Kaplan Executive Function System Letter Fluency test (p = 0.003), and Symbol Search subtest from the Wechsler Adult Intelligence Scale-IV (p = 0.009). However, the study had some important limitations, which included a lack of assessing cognitive dysfunction (either self-report or neurocognitive assessment) to determine study eligibility. The authors report this could have biased results, as individuals who enrolled may have had higher cognitive function and thus higher interest in participating in the study, and may therefore have been responsive to treatment. In addition, there was no active treatment control condition and no follow-up to assess outcome sustainability. The treatment did not require a trained clinician to administer it, but did consist of four to five 20–30 minute unsupervised practice sessions weekly for 12–15 weeks.

The range of "dosing" could vary from 16 to 30 hours of training and it remains unknown how much practice is necessary to have a positive clinical effect [145, 147]. While computerized interventions appear convenient (requires no clinical staff, space, or office visit by the survivor) they also may be limited in generalizability of survivor memory skills to real-world task performance, and may still require much time in practice to achieve positive outcomes. Finally, they may not be attractive to survivors who prefer interpersonal interaction over an electronic intervention [148].

Cognitive-behavioral therapy (CBT) has also been developed and evaluated as a treatment for CRCD. Memory and Attention Adaptation Training (MAAT) is brief CBT and has been evaluated in three studies of BCS [149–151], one study with individuals after mild to severe traumatic brain injury where MAAT was evaluated in combination with methylphenidate or pill placebo [152], and an additional study of MAAT modified and combined with problem solving for individuals with epilepsy [153]. In its current form, MAAT consists of 8 weekly visits of 30–45 minutes in duration. Clinicians follow a manualized protocol while survivors are provided a workbook to aid in review and retention of material covered in visits and guide daily application of compensatory skills. MAAT consists of 4 components: (1) *Education on CRCD* and with emphasis on modifying causal attributions for daily memory failures from cancer-related causes to the possibility of more controllable causes of stress and inattentiveness [154–156]. This causal attributional shift may enhance coping [157]; (2) *Self-awareness training* that utilizes self-monitoring to help survivors identify "at risk" contextual, cognitive, or emotional conditions under which cognitive failures occur; (3) *Compensatory strategy training* to improve daily cognitive task performance. Examples include Self-Instructional Training (SIT) [158], using a day planner, active listening and visualization strategies [159]; and (4) *Stress management*, including self-regulation skills, activity scheduling/pacing and cognitive restructuring to modify negative appraisals of cognitive failure [150, 160, 161].

MAAT was developed after extensive literature review of treatments for cognitive dysfunction [154, 157, 162–168] (Fig. 11.2). It emphasizes acquisition of adaptive behavioral, emotion regulation, and cognitive skills to optimize cognitive performance and emotional coping with cognitive dysfunction in daily life [160, 166, 168, 169]. CRCD symptoms can be worse under conditions

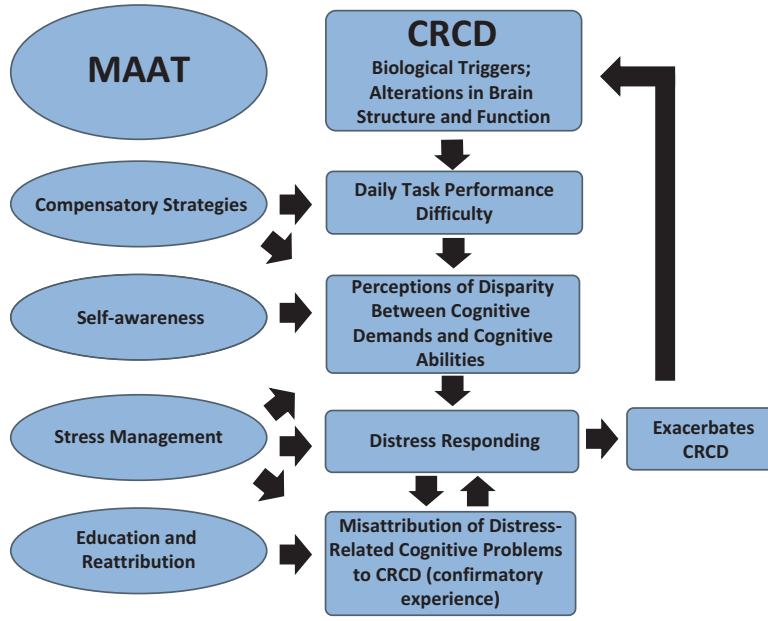

Fig. 11.2 Diathesis-stress and appraisal model of CRCD and MAAT components of change

of increased task demand. As task demands increase (e.g., work or family demands), there is a theoretical rise in the *perceived* disparity between task demand and cognitive abilities to meet task demands [69, 79, 170]. This perceived deficit in ability to meet demands leads to increased psychophysiological arousal and emotional distress, and ultimately exacerbates cognitive interference and can result in confirmatory experience of cognitive failure. Thus, the acquisition of self-regulation and compensatory cognitive skills can enhance ability to meet rising task demands, enhance performance self-efficacy, and reduce distress about cognitive symptoms as they occur in real-world settings [147, 165–167, 171, 172]. This theoretical conceptualization of MAAT is depicted in Fig. 11.2 [170].

Empirical support for MAAT among BCS has accumulated over the course of three studies, with the first study as a single group design (feasibility study) that showed improvements in verbal memory, processing speed, self-reported cognitive complaints and quality of life measures (see Table 11.1) [149].

A second study with improved methods utilized a waitlist (no treatment) randomized controlled trial (RCT) design [150]. Results demonstrated significantly improved verbal memory (California Verbal Learning Test-II) and quality of life among 19 BCS randomized to MAAT over 21 randomized to the waitlist (survivors were at least 18 months post-chemotherapy). In the third MAAT study, MAAT was expanded from a 4 visits and 3-phone contact intervention format to an 8-visit (30–45 minutes) format with the intention of videoconference delivery. The RCT design was improved by adding an active control condition, supportive therapy (ST) [151], to control for therapeutic "common factors" such as interpersonal warmth, empathy, and treatment expectation influences on outcomes. The primary self-reported outcome measure was the Functional Assessment of Cancer Therapy-Cognitive scale (FACT-Cog) [173].

Both MAAT and ST were delivered via videoconference network linking rural health centers to evaluate MAAT efficacy with telehealth delivery [151, 174]. Adjusting for baseline differences, MAAT participants improved in FACT-Cog perceived cognitive impairments over ST at 2-month follow-up (p = 0.02; d = 0.52; trend at post-treatment p = 0.09). In neurocognitive outcomes, MAAT participants made significant improvement in processing speed over controls at post-treatment (p = 0.03; d = 0.50) but not on verbal memory. MAAT participants also

Table 11.1 Three MAAT studies with breast cancer survivors from 2007 to 2016

Study	Design	Sample, N	Primary self-reported outcomes	Primary neuropsychological outcomes
Ferguson et al. [149]	Single group repeated measures; BL, PT, 2M and 6M f/u	29 Stage I and II BCS, at least 3 years post- treatment	*MASQ*: Improvements over BL at PT, 2M, 3M *QOL-Total*: Improvement over BL at 6M	*CVLT-II*: Improvements over BL at 2M, 6M *Logical Memory I & II*: Improvements over BL at PT, 2M, 6M *Stroop*: Improvements over BL at PT, 2M, 6M *Digit Symbol*: Improvements over BL at 2M, 6M
Ferguson et al. [150]	Randomized Controlled Trial (RCT) with Waitlist (WL) Control; BL, PT, 2M f/u	40 Stage I and II BCS at least 18 months post- treatment	*MASQ*: ns between MAAT or WL at PT, 2M; However, MAAT 13.02 point improvement at PT, vs. 6.21 for WL at PT. *QOL*- Spiritual MAAT > WL at PT	*CVLT-II*: Improvement over WL at PT, 2M *Stroop, Digit Symbol*: ns
Ferguson et al. [151]	RCT with attention control (Supportive Therapy; ST); BL, PT, 2M f/u	47 Stage I, II and IIIa BCS at least 6 months post-treatment (final analysis N = 35)	*FACT-Cog PCI*: MAAT > ST at 2M; $p = 0.02$ MAAT > ST at PT, ns, $p = 0.07$ *MIA-A*: MAAT > ST at 2M, $p = 0.09$	Telephone Administered: *CVLT-II*: ns; however, MAAT improvement 4.1 points vs. ST 2.2 *Symbol Digit*: MAAT > ST at PT

BCS Breast Cancer Survivors
Time points: *BL* Baseline, *PT* Post-Treatment, *2M, 6M* 2 or 6 month follow-up time points
Outcomes: *CVLT-II* California Verbal learning Test-II, Total Score; *MASQ* Multiple Ability Self-Report Questionnaire, *QOL* Quality of Life-Cancer Survivor

had a trend ($p = 0.07$) for improvement over ST in anxiety about cognitive symptoms (Meta-Memory in Adulthood Anxiety Scale) with a large effect size ($d = 0.90$) at 2-month follow-up. This suggests MAAT participants continued to make gains in emotional distress reduction while ST participants regressed to baseline 2 months after cessation of therapeutic contact.

However, the study described above was underpowered with limitations to expand recruitment of volunteer participants and extend the study for a larger sample. This limits confidence in the result that MAAT has a strong effect on reduction in anxiety about cognitive problems above and beyond ST. Nevertheless, MAAT participants reported high satisfaction with MAAT and they were more likely to recommend MAAT to a friend than ST participants were to recommend ST to a friend. In addition, 75% of MAAT participants indicated they likely would have not been able to engage MAAT without videoconference delivery, suggesting this mode of treatment delivery improves access for survivorship services.

While promising, limitations of MAAT research for cancer survivors include small sample sizes, restrictions of research to only BCS, and one clinician per MAAT or ST control condition. More research with MAAT utilizing large samples of cancer patients at multiple sites with multiple clinicians is needed to add to confidence in generalizability of treatment. In addition, longer follow-up time points of 6–12 months and with other types of cancer survivors would help determine sustainability of positive outcomes and for individuals with different forms of cancer. MAAT has been evaluated in a multi-site, multi-clinician RCT among 71 male and female participants with persistent cognitive problems after traumatic brain injury [152]. This approach could be replicated among cancer survivors. The trial involved a 2 × 2 research design comparing

MAAT combined with either methylphenidate or pill placebo with a behavioral, repetitive task "behavioral placebo" ("Attention Builders Training"). In short, MAAT demonstrated improved word-list learning over behavioral placebo, and in combination with methylphenidate improved nonverbal learning and auditory working memory and divided attention over behavioral placebo with methylphenidate [152]. Perhaps MAAT combined with MPH could be helpful for cancer survivors of many different forms of cancer including those with both CNS and non-CNS disease.

Physical activity may also improve cognitive function in individuals with cancer [175, 176]. Growing evidence suggests that physical activity improves cognitive function in healthy older adults [177, 178]. Physical activity is associated with increased hippocampal volume, reductions in pro-inflammatory cytokines including IL-6, CRP, and TNF-α, and increases in brain derived neurotrophic factor (BDNF) [179]. Physical activity is also associated with reduced depressive symptoms, anxiety, fatigue and sleep problems; symptoms that commonly co-occur with CRCD [180, 181]. There is one review of 19 studies on effects of exercise on CRCD. Five of the studies in that review were with rodents and of the 14 studies on humans, only 6 were randomized controlled trials [182]. The authors conclude that current data suggest that Asian movement exercise (e.g., yoga) has benefits for self-reported cognitive impairments and reductions in inflammation among BCS. More research is needed to determine whether the benefits of exercise in older adults extend to individuals with cancer.

11.4.2 Pharmacotherapy

Drug interventions for CRCD have also been investigated. For example, an 8-week double-blind, placebo-controlled trial of dexmethylphenidate (d-MPH; mean of 27.7 mg/day) was conducted with 152 adult patients with various cancers (excluding primary or metastatic CNS tumors) [183]. Improvements in fatigue and the memory score of the Highly Sensitive Cognitive Screen were observed among active medication participants vs. placebo. However, that trial consisted of only baseline and post-treatment assessment at the end of 8 weeks. No follow-up assessment occurred and there was no self-reported cognitive function or quality of life measure. Thus, it is not known if d-MPH produces long-term gains in neurocognitive and quality of life outcomes among BCS. In another study, a sample of 68 BCS with CRCD (mean of 22.8 months after last treatment) completed a trial of modafinil vs. placebo [184]. Participants were assessed with the Cognitive Drug Research computerized neurocognitive assessment and the Brief Symptom Inventory at baseline and after 4 weeks. Significant improvements in the Speed of Memory Index (p = 0.0002) and Digit Vigilance subtests of the CDR were observed in modafinil participants. No significant gains were observed in the placebo group. Results suggest some clinical benefit for modafinil in processing speed and attention. However, there was no long-term follow-up assessment or report on measures of fatigue.

The long-term effects of modafinil on neurocognitive outcomes remain unknown. In summary, there is incomplete evidence that pharmacotherapy offers cancer survivors relief from CRCD [139]. Perhaps most important, survivors appear to prefer effective non-drug alternatives after cancer treatment, either to reduce the number of medications taken or minimize side effects [70, 185]. For instance, in the d-MPH trial, 40.8% of participants reported mild/moderate headache and 27.6% reported nausea. In light of our poor understanding of the etiology of CRCD and potential for unpleasant side effects, emphasis might be placed on continued development of non-pharmacological approaches as low-risk alternatives until a better understanding of CRCD mechanisms comes to light.

11.4.3 Treatment Dissemination

There is increased awareness of CRCD and its adverse effects among medical oncologists, with 55% of cancer survivors reporting their oncologist as understanding about the problem.

However, only 10% of survivors report being offered assistance [138, 186, 187]. This is most likely due to the fact there are few established treatments currently available. CRCD is complex, it does not affect all survivors, and evidence of efficacy for various treatment approaches continues to be gathered at the time of this publication.

There are also few clinicians trained to deliver existing treatments for CRCD (e.g., MAAT or computerized methods) and treatment dissemination is therefore slow, as health professionals choose which treatment approaches to adopt. Fortunately, more attention is being paid to CRCD treatment research that addresses methodological limitations noted above to improve the knowledge of CRCD treatment efficacy [139, 141, 143]. However, RCTs in this area in particular are expensive and take much time to complete, delaying compilation of CRCD treatment knowledge. Perhaps one method of supplementing CRCD treatment research based on the gold-standard RCT is to take advantage of newly available electronic outcomes monitoring systems, such as the U.S. National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS).

These outcomes monitoring systems can provide valuable information about real-world effectiveness of available treatments of CRCD [188]. For example, a centralized, secured web-based data repository for self-reported outcomes could be maintained to evaluate CRCD treatment outcomes among individual survivors or cohorts of survivors (e.g., by disease type, cancer therapy type, or age-related categorization) and use single case or multiple baseline experimental designs to evaluate treatment efficacy [189–191]. These methods could be used with archival data to answer important questions about treatment efficacy among survivors with medical (e.g., heart or vascular disease, previous brain injury) or psychiatric comorbidities that would otherwise make them ineligible for RCTs. This type of outcomes monitoring would provide detailed information to guide treatment improvement and ultimately help determine which type of CRCD treatment is best suited to individual survivors.

11.5 Cognitive Dysfunction Associated with CNS Disease

In addition to cognitive dysfunction associated with non-CNS cancers and systemic treatments, primary CNS disease is associated with more severe cognitive dysfunction due to direct disruption and pathology in the brain. The effects of treatment of CNS disease can be more severe as well, as treatments, including resection, intrathecal chemotherapy, and partial or whole brain radiation, are limited in their ability to target only diseased tissue in the brain, similar to systemic treatments for non-CNS cancers, but with direct effects on otherwise healthy brain tissue. In this section we describe incidence of CNS disease, cognitive changes associated with diagnosis, and effects of surgical resection, radiotherapy, and chemotherapy used in treatment of the disease.

11.5.1 Background and Prevalence

Central nervous system tumors may either be primary, originating and developing within the CNS, or metastatic, originating in non-CNS tissue and migrating to the CNS. The incidence of primary brain tumors is estimated to be 22.36 per 100,000 across age groups, 5.7 per 100,000 in children (0–19 years), and 29.18 per 100,000 in adults (20+ years) [192]. Primary CNS tumors are classified by location and cell histology, with gliomas, arising from glial cells including astrocytes, ependymal cells, and oligodendrocytes, representing the most common classification. Gliomas may be classified as high grade (glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic mixed glioma) or low grade (astrocytoma, oligodendroglioma, and mixed glioma). In addition to gliomas, other primary CNS tumors include meningioma, medulloblastoma, and primary central nervous system lymphoma.

The most common site of primary CNS tumor proliferation regardless of malignancy is in the meninges (37% brain or spine). Organized by lobe in descending order, the most common sites are frontal (8%), temporal (6%), parietal (4%),

and occipital (1%) involvement. Pituitary and craniopharyngeal duct tumors are also relatively common (17%). For non-malignant tumors, the meninges are the most commonly affected (53%). For malignant tumors, the most common site of involvement is in the frontal lobes (23.6%), followed by temporal (17.4%), parietal (10.6%), and occipital (2.8%) involvement.

Metastatic disease from other organs to the brain is also a significant concern. The incidence of metastatic CNS disease has been estimated over a wide range, potentially due to variability in reporting systems and data sources [193, 194]. Previous work in a uniform sample reported total incidence proportions of 9.6% [195]. With regard to primary cancer sites with metastatic risk to the CNS, lung (non-small cell lung cancer, small cell lung cancer) was highest (19.9%), followed by melanoma (6.9%), renal (6.5%), breast (5.1%), and colorectal (1.8%) cancers [195], with no clear differential effect of primary tumor site on cognitive dysfunction.

11.6 Diagnosis and Treatment Related Effects of CNS CRCD

11.6.1 Acute and Pre-treatment

Acute symptoms related to CNS tumors include headaches, focal neurological signs, new onset seizures, and cognitive dysfunction related to tumor location. Unsurprisingly, previous studies have reported cognitive dysfunction in newly diagnosed patient groups prior to treatment [196], including in patients who otherwise present as neurologically normal [197]. A recent systematic review of cognitive dysfunction in diffuse glioma patients prior to anti-tumor treatments found impairment in 62.6% of patient in at least one domain [198]. Temporal and frontal involvement has been associated with deficits in 90% of patients prior to treatment, with 78% of patients exhibiting executive dysfunction, and 60% exhibiting attention and recall deficits [199]. Tumor volume, anterior location, and dominant hemisphere involvement have been found to be associated with worse executive functioning, verbal fluency, psychomotor speed, and short-term and long-term memory [197].

11.6.2 Resection

Cognitive effects of surgical resection are generally predicted by tumor location and amplified by edema and resection of intact tissue. As discussed above, cognition prior to surgery is altered both due to potential mass effect of tumor growth and cerebral edema, as well as a result of disruption of circuits due to infiltrating tumor growth. There have been relatively few studies that prospectively assessed cognition before and after resection. As a result, pre-resection cognitive dysfunction related to tumor location has been difficult to distinguish from the effects of resection. Gross effects of resection that includes so-called "eloquent" areas (motor, somatosensory, visual, Broca, and Wernicke areas) are more easily identified, but these do not address finer aspects of cognition such as higher-order cognitive abilities (executive functioning; learning and memory; generativity, etc.). In previous studies that have assessed cognition prospectively, stable or relatively improved functioning has been reported following surgery in both low-grade and high-grade glioma resection, with a subset of studies demonstrating declines [200].

A more recent systematic review of 17 prospective studies also suggests inconsistency in longer-term outcomes following resection, finding an acute decline in cognition immediately following surgery followed by improvement over shorter intervals and mixed findings of both improvement and decline at longer intervals [201]. This points to the difficulty in adequately describing a "typical" course with respect to primary CNS cancer, as baseline characteristics and post-resection functioning will be especially affected by the variability of tumor location and volume, resection location and extent, mass effect, presence of edema, and individual differences in pharmacologic effects (e.g., anti-epileptics) and potential involvement of healthy tissue.

11.6.3 Whole Brain and Prophylactic Cranial Irradiation

Fractionated whole brain radiation therapy (fWBRT) is used in both metastatic disease and in conditions in which multiple tumors are present or where surgical resection is not possible. fWBRT applies an external beam to the whole brain in fractionated doses (i.e., multiple treatments of lower dose radiation to achieve a total dose at completion). Radiation effects have been classified as acute, early-delayed, and late-delayed injury [202, 203]. Acute effects are less common with contemporary treatments, whereas reversible, early-delayed effects (1–6 months following treatment) may include underlying demyelination and somnolence.

Late-delayed injury (>6 months post-treatment) includes demyelination, vascular abnormalities, and white matter necrosis [202]. As a result of late-delayed effects to the CNS, longer-lasting and potentially irreversible cognitive dysfunction is identified in this time-frame. Late effects may be predicted by the volume of radiated tissue, radiation dose, age, combined chemotherapy treatment, and vascular risk factors. The pattern of cognitive deficits associated with whole brain radiation therapy is generally diffuse, and associated with declines in learning and retrieval of new information, executive dysfunction, inattention, and psychomotor slowing [204–210]. Underlying mechanisms that have been considered in late-delayed effects include vascular damage in the form of thickening of vessel walls, dilation, and effects on endothelial function that together lead to ischemic changes and resulting white matter damage. Also considered is the effect of radiation on several CNS cell types, including damage to oligodendrocyte progenitor cells leading to disrupted myelin production and resulting white matter damage; activation of astrocytes leading to increased inflammatory response and disrupted blood-brain barrier integrity; and chronic activation of microglia leading to chronic inflammatory processes and oxidative stress in the CNS [202].

Similar to fWBRT, prophylactic cranial irradiation (PCI) applies an external beam to the whole brain to treat potential occult tumor cells that may have metastasized in cancers that commonly spread to the CNS (e.g., small cell and non-small cell lung cancer), but in the absence of proven evidence of metastasis. PCI has been found to be associated with cognitive declines in the Radiation Therapy Oncology Group (RTOG) 0214 randomized clinical trial [211], with significant declines in learning and memory in the PCI-treated group compared to observation [212], and declines in self-reported quality of life [213]. Similar findings were reported in relation to PCI in a European cohort [214]. Given the findings of significant cognitive effects of WBRT and PCI, attempts to reduce radiation dose to areas supporting learning and memory, with a particular focus on bilateral hippocampi, have been introduced.

11.6.4 Hippocampal Sparing Radiotherapy

Previous animal studies have found that external radiation may have a specific effect on hippocampal neurogenesis in radiation-exposed non-human animals [215, 216]. The translation of hippocampal radiation exposure to human-level learning and memory performance has been confirmed in prospective studies examining varying doses of hippocampal radiation exposure, with greater hippocampal exposure predicting lower learning and memory performance both in pediatric [217] and adult [218] patient groups. Hippocampal sparing PCI or WBRT applies a conformal external beam with the aim of targeting areas outside of hippocampal and medial temporal regions. A benefit of intentionally sparing hippocampal areas was found in the RTOG 0933 trial, which contrasted traditionally treated WBRT historic controls with patients undergoing hippocampal-sparing WBRT (hs-WBRT) for brain metastases [219]. The authors reported a 7% decline in learning and memory performance at 4 months in the HS-WBRT group compared to 30% decline in historic controls. Similar results were reported for a mixed group of PCI- and WBRT-treated patients with hippocampal sparing treatment, finding an association of verbal

learning and memory with dose escalation to hippocampus and generally preserved cognitive functioning at follow-up [220].

11.6.5 Stereotactic Radiosurgery

Efforts have been made since the introduction of radiation therapies to more focally target radiation treatments to affected tissue and in so doing to better preserve cognitive functioning. Stereotactic radiosurgery (SRS), in which multiple, weaker external beams converge on the intended target while sparing areas outside the target, has been used to this end. A handful of recent studies have investigated cognitive outcomes, tumor progression, and overall survival between SRS alone or combined with WBRT. In a recent study documenting the effects of SRS versus SRS/WBRT on cognitive function [221], improved cognitive outcomes were found in learning and memory performance with increased tumor progression in the SRS group but with no significant difference in survival. Similar results were found in a smaller study that contrasted cognitive outcomes between SRS and SRS/WBRT, with the study stopping early due to the significant decline in total recall when WBRT was combined with SRS [222]. In contrast, two studies [223, 224] found relatively better functioning when treatments were combined, although cognitive assessment was restricted to only mental status testing and therefore may have been insensitive to higher-order cognitive decline.

11.6.6 Chemotherapy

While to a lesser extent than non-CNS cancers, chemotherapy has also been used in the treatment of cancers in the CNS. Chemotherapy may either be administered systemically as in non-CNS cancers, or intrathecally (i.e., directly introduced to cerebrospinal fluid). Specific agents include: temozolomide; carmustine; combined procarbazine, lomustine, and vincristine; irinotecan; platins; methotrexate; and cyclophosphamide. Toxicity in the CNS may present as acute, subacute, or chronic encephalopathy, seizures, headache, vascular changes, sensory alterations, and myelopathy [225]. Longer-term and more subtle effects of chemotherapy in CNS cancers have also been demonstrated, potentially as a result of demyelination, vascular alterations, inflammatory response, and oxidative stress [149]. Direct damage to multiple cell types has been demonstrated in previous work [226], and in hippocampal regions (subventricular zone; dentate gyrus) specifically [227, 228]. The effects of chemotherapy treatment may be amplified when combined with radiotherapy, potentially due to increased radiosensitivity, combined toxic effects on brain tissue, and/or increased blood-brain barrier permeability [229].

11.7 Impact on Quality of Life

Self-reported quality of life outcome measurement has become an important goal in the post-treatment phase and/or in cancer survivorship [230]. As the discussion of disease and treatment effects above makes clear, quality of life (QOL) for patients with either primary CNS cancer or metastasis to the CNS is significantly affected. In a recent, large meta-analysis of quality of life and resource utilization in patients with brain metastases, CNS involvement was unsurprisingly associated with poorer quality of life, and WBRT was associated with either stable or lower QOL, rather than improvement. These results are difficult to interpret, since, as the authors note, included studies do not contrast the effect of brain metastases versus no metastatic disease, or treated versus untreated brain metastasis. With regard to self-reported versus objective performance agreement in CNS cancer, previous studies have found moderate associations between self-reported and objective cognitive functioning, irrespective of fatigue or other mood variables [196, 231, 232]. Importantly, self-reported functioning has historically been an imperfect predictor of objectively measured cognitive dysfunction, which may suggest insensitivity of objective performance measures or the potential that self-report measures are influenced by other factors

(e.g., depression, stress, anxiety), among other scenarios. A recent study in patients with stable gliomas (stage II and III) found an association between self-reported cognitive function and fatigue and mood factors, rather than with objective performance measures [233].

11.8 Treatment Approaches

Efforts at minimizing the effects of CNS disease and treatment on cognitive functioning have been made broadly in the form of behavioral and educational approaches or through pharmacotherapy (see Table 11.2).

11.8.1 Non-pharmacological Approaches

Similar to rehabilitation in non-CNS cancers, non-pharmacologic treatment in CNS cancer typically consists of either direct "restorative" approaches or compensatory "prosthetic" approaches aimed at ameliorating cognitive dysfunction. Direct approaches often utilize repetitive training of cognitive tasks targeting underlying neural circuits that support a given cognitive function, with the expectation that improvement in the focused task will generalize to other situations that require this ability. Compensatory approaches generally train and educate individuals in alternate strategies in completing common cognitive tasks and utilize cognitive scaffolding techniques, mnemonic devices, and cognitive aids (to-do lists, smart phone use, calendars, alarms, etc.), similar to components of MAAT as discussed previously [239, 240].

Both approaches have yielded some positive outcomes in rehabilitation in CNS cancer survivors, although again there is significant variability given the heterogeneity of tumor location, extent, and treatments [241, 242]. Additionally, difficulties associated with accrual and attrition limit interpretability of previous findings [243]. In a compensatory training study involving 13 brain tumor patients, significant gains in functional independence were found in half of the patients following 3 weeks to 4 months of training [244]. In a novel approach using patient/caregiver dyads and training in problem solving and memory, half of all patients reported using the new strategies, but no significant effect on quality of life or functional capacity was found [245]. In a large, randomized controlled trial in a mixed compensatory and computer training rehabilitation program, significant improvements in self-reported cognitive abilities were found but with no corresponding increase in objective measures of cognition; improved objective performance in verbal memory and attention was found at the 6-month follow-up time-point but self-reported gains were absent [240].

11.8.2 Pharmacotherapy

Donepezil, an acetylcholinesterase inhibitor originally designed for use in Alzheimer's disease, has been used in the setting of primary CNS cancer for treatment of cognitive dysfunction following radiotherapy. Three studies have used donepezil in primary CNS disease. In a Phase II, single-arm cross-over study that used donepezil in patients following WBRT, improvements were exhibited in both self-reported cognition and objective performance (attention, verbal and figural memory) together with improvements in mood symptoms [246]. In a follow-up Phase III study, which included a placebo-control group [235], donepezil-treated patients exhibited significantly better performance in recognition memory and psychomotor speed. When assessed by level of pre-treatment impairment, the lowest performing group was the most significantly improved on donepezil (composite scores of immediate recall, delayed recall, attention, visuomotor skills, and psychomotor speed). A more recent longitudinal study examined the effects of donepezil in CNS cancer survivors over three time points and found improved functioning in attention, psychomotor speed, and visual memory, together with self-reported QOL [247]. Donepezil may hold promise for patients with CNS disease who exhibit more severe neurocognitive and quality of life impairments.

Table 11.2 Treatments for CNS-CRCD

Pharmacologic				
Boele et al. [234]	37 primary brain tumor	Cross-over modafinil versus placebo	Objective and subjective measures	Improvements in fatigue, motivation, physical health, working memory and information processing in both placebo and modafinil.
Rapp et al. [235]	198 primary brain tumor or metastases	Donepezil versus placebo	Objective measures	24 weeks of active treatment resulted in increased recognition memory, motor speed and dexterity. Greater effect in patients with lesser pre-treatment cognitive function.
Brown et al. [236]	508 brain metastases; 149 analyzable at 24 weeks	Memantine versus placebo during radiation therapy	Objective measures	Preserved executive function at 8 and 16 weeks, and psychomotor speed and recognition memory at 24 weeks in the memantine group. Lesser rate of cognitive failure at 24 weeks in memantine (53.8%) versus placebo (64.9%)
Butler et al. [237]	69 primary or metastatic brain tumors	d-methylphenidate versus placebo	Objective and subjective measures	Study stopped early due to slow accrual and no interim effect on 68 patients
Behavioral				
Gehring et al. [238]	140 low-grade and anaplastic glioma	Intervention versus wait-list control	Objective and subjective measures	Computer based attention retraining; compensatory skill acquisition resulted in post-treatment improvement in subjective cognitive function, 6-month improvement in objective attention and verbal memory

Methylphenidate, a psychostimulant most typically used in the treatment of attention deficits such as those seen in attention-deficit/hyperactivity disorder, have also been used in the setting of primary CNS cancer for treatment of cognitive dysfunction, although previous literature is limited. Early reports in case series or smaller samples indicated generally positive effects of methylphenidate on cognitive function, and on ratings of fatigue, motivation, and energy [248, 249]. Relatively little has been published since these two early articles, but a Phase III placebo-controlled clinical trial in brain tumor patients receiving prophylactic dexmethylphenidate throughout radiotherapy found no significant effect of drug on either self-reported cognition or mental status testing [237].

Memantine, an NMDA receptor antagonist, has exhibited neuroprotective properties in non-human animal samples potentially due to reduced excitotoxicity related to NMDA stimulation via glutamatergic excitation. The RTOG 0614 trial tested potential prophylactic effectiveness of memantine in patients undergoing WBRT and found reduced rate of decline in memory, psychomotor speed, and executive function, but not significant differences in magnitude of decline [236]. In a pilot study, evidence of neuroprotective effects of memantine throughout radiotherapy using dynamic contrast-enhanced MRI found reduced changes to normal-appearing white matter in the memantine-treated group [250].

Modafinil, a wakefulness promoting agent used for the treatment of narcolepsy, has been used in the treatment of fatigue and cognitive dysfunction associated with radiation therapy. In an early pilot trial, positive effects were demonstrated in a single arm across fatigue, mood, and cognitive measures [251]. A placebo cross-over study, however, failed to find a significant effect in any outcome measure [234]. A small study examining benefits of either methylphenidate or modafinil found no significant differences between groups but did find a main effect of treatment on improvement in executive functioning and psychomotor speed [252]. Armodafinil acts, unlike modafinil, as a dopamine receptor antagonist and reuptake inhibitor. A recent Phase

II placebo controlled trial in patients receiving radiotherapy found no significant effect on self-reported measures of QOL or cognitive function [253].

While meant to control seizures following treatment, anti-epileptic medications may have independent effects on post-treatment cognitive function. Adequate control of seizures may be associated with relatively preserved cognition absent recurrence or progression of disease. On the other hand, anti-epileptic drugs can also have a negative effect on cognition and the balance of these effects with seizure control must be assessed [254].

11.9 Future Directions

The problem of CRCD remains a growing area of research in cancer survivorship for both non-CNS and CNS cancers. As emphasized in the introduction, the public health concern that CRCD raises is somewhat daunting given the projected growth of cancer survivors in the US to about 20 million by 2026 [8]. While much has been learned, future areas of research can help clarify the various types of CRCD, the underlying mechanisms, and ultimately the best clinical management strategies that match individual survivor presentation. Specific directions at this time that can provide the most "yield" in research efforts include:

1. Evaluation of mechanisms of direct neurotoxic effects, DNA damage, cytokine dysregulation, or inflammation in basic research which can then help guide development of protective/preventive therapies or pharmacologic agents;
2. Evaluation of genetic influences and genomic profiling that can lead to understanding of vulnerability to CRCD—whether the CRCD source be non-CNS or CNS cancer itself, systemic chemotherapy, surgery, radiotherapy or immunotherapies;
3. Research and development of improved computerized neurocognitive assessment that is validated with neuroimaging technologies to help identify a more complete understanding of degree of impairment and underlying mechanism of cognitive change;
4. With more efficient neurocognitive tracking tools, using such instruments to evaluate the impact of newly developed therapies, such as immunotherapies that are often associated with "cytokine syndrome." These new neurocognitive assessment technologies can be less intrusive into cancer-treatment clinical trials and thus may more easily included as a quality of life measure superimposed on existing cancer treatment trials;
5. Continued research on the efficacy of various CRCD treatment approaches, such as cognitive rehabilitation using computerized technology, CBT, pharmacotherapy, and physical activity, identifying which cancer survivors benefit most from which treatment, and evaluating preventive strategies.

These five areas of CRCD research may yield better functional and quality of life cancer outcomes and minimize cancer-related disability. Working closely with policy makers and survivor advocacy groups will likely produce the best results for increased awareness and funding for this important area of cancer survivorship.

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Work

12

Diane Von Ah, Saskia Duijts, Peter van Muijen, Angela de Boer, and Fehmidah Munir

12.1 Introduction

In the last decade, cancer in the workplace has received growing attention worldwide [1, 2]. Surviving cancer diagnosis and treatment have led to a recognition that remaining at work during cancer treatment, returning to work following treatment or remaining in the workplace as an employee with a history of cancer and its treatment can be a viable and meaningful goal [3]. Nevertheless, the number of new cancer cases (i.e., approximately 14 million in 2012) is expected to rise globally by 70% (to 22 million) over the next two decades [4, 5]. An estimated 40–50% of these worldwide cancer diagnoses occur in people who are 65 years of age or younger, who are potentially part of the labor force [4, 6], and challenges continue to help survivors benefit from a productive work life.

The first studies in which issues related to cancer and work were addressed originated from the mid-1970s and mainly reported about discrimination and health insurance problems encountered by cancer patients and survivors [7, 8]. In the following decades, i.e., the 1980s and the 1990s, a change in tone and issues took place, and research was primarily aimed at identifying factors impacting return to work (RTW) in this patient population. Moreover, the majority of intervention programs, attempting to affect the RTW process of cancer survivors, have predominantly been developed and evaluated from 2000 and onwards [9]. While both the quality and the quantity of scientific studies regarding cancer patients' returning to work have taken a turn for the better, recent literature suggests that the impact of cancer on patients' work-related functioning is still immediate and striking [10]. For example, cancer survivors in general are more likely to be unemployed than healthy control participants (33.8% vs.

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15.2%; pooled relative risk [RR], 1.4; 95% confidence interval [CI], 1.2–1.6) [11]. In addition, breast cancer survivors experience a higher risk of losing paid employment (hazard ratio [HR]: 1.6, 95% CI 1.4–1.8) or any work-related event up to 5–7 years (HR 1.5, 95% CI 1.3–1.6) and of receiving disability benefits up to 10 years after diagnosis (HR 2.0, 95% CI 1.6–2.5) [12].

Although most research in the area of cancer survivorship and work centered on RTW of those who are part of the labor force, it is clear that there is a considerable range in investigating work-related outcomes worldwide. For example, previous studies focused on the probability and timeliness of returning to work, but also on outcomes such as employment status (e.g., having paid work [full-time/part-time], being self-employed, being unemployed), work ability, job performance, productivity, job loss, sick leave, duration of absence, working hours, work changes, retirement, voluntary work, as well as physical and psychological disability [13]. Potential inconsistency in defining these outcomes, and existing differences between social insurance systems among countries remain an ongoing challenge when comparing international scientific findings within the field of cancer and work.

Over the past 40 years, important steps forward in aiding and supporting cancer patients and survivors in their RTW have been made. Today, returning to work and even continuation of work during treatment are no longer the exception. About 62% of cancer patients and survivors are able to RTW within 12 months after diagnosis, up to approximately 89% 2 years post-diagnosis [13]. Also, previous research reveals that cancer survivors who are able to (return to) work and subsequently stay at work for at least 1 year, function better and have a better health and quality of life than those who are not able to (return to) work [3]. However, while these findings are promising, more attention should be given to the work situation of specific groups of cancer survivors, such as those unemployed or self-employed. Since the number of these survivors are expected to increase in the future, it is essential to identify new methods of work support for them [14].

In general, most cancer patients and survivors are highly motivated to RTW, after a period of sick leave, which can vary by country. Employment participation is often viewed as a sign of recovery, and a vital aspect of re-establishing normality and quality of life [15, 16]. From the individual's viewpoint, not returning to work may lead to financial losses, social isolation and a decrease in self-esteem [17, 18]. From the societal perspective, it is of utmost importance to reduce avoidable work incapacity and consequent productivity losses [19]. Therefore, it is essential to consider how to make the patients' transition back to work as unproblematic as possible. To meet this goal, this chapter describes the main points that have been addressed in research so far. Among others, an overview of factors influencing RTW and continuation of work post treatment is provided, as well as evidence based approaches and interventions for managing work problems in cancer survivors. Latest developments and changes in policies worldwide are discussed and necessary future steps are outlined.

12.2 Conceptual Models of Work

Multiple conceptual models were proposed to help explain the relationship between disability and work [20–22]. A recent model, The Cancer Survivors and Work Model, is a comprehensive and evidence-based conceptual model, which provides a framework describing the on-going relationships among health and well-being, symptoms, functional limitations, work demands and work outcomes in cancer survivors to provide a way to look at cancer survivorship and work clinically and in future research. The model describes a potential pathway linking survivor characteristics, post-treatment sequelae, including the impact of symptoms, job demands, the work environment, workplace and societal policy and procedures to various work outcomes (See Fig. 12.1) [21]. This model has helped support research to identify factors that influence RTW and other work-related outcomes. In the next

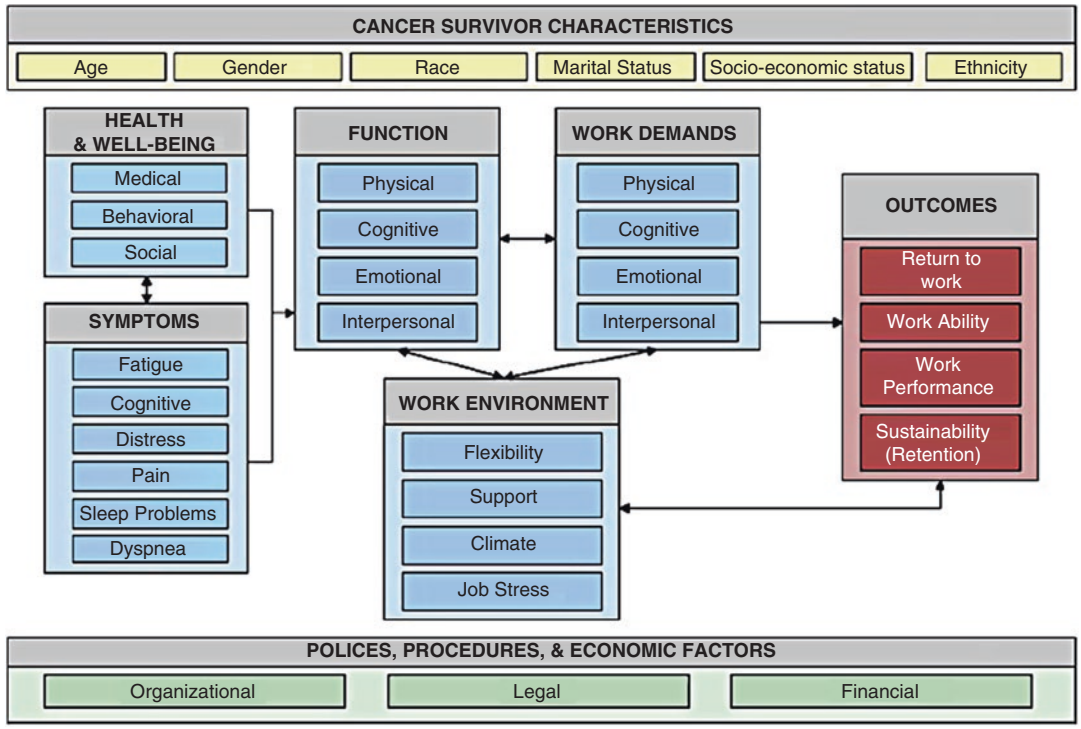

Fig. 12.1 Cancer survivorship and work: conceptual framework. (From. Feuerstein et al. [21]. Reprinted with permission)

section, we review the latest research exploring factors that influence work.

12.3 Factors Influencing Work

Previous studies on cancer survivorship and employment participation identified a number of factors that relate to RTW in cancer survivors [13, 23–25]. These factors are generally categorized as disease-related factors, work-related factors, and finally, as factors related to the person or the environment [26]. In counseling cancer survivors who wish to RTW, one must be aware of the fact that various factors can play a role simultaneously, that these factors may impede either physical, cognitive and/or social functioning of cancer survivors, and that, if possible, they need to be addressed in order to enhance vocational rehabilitation.

12.4 Disease-related Factors

Tumor site, stage and burden of disease (e.g., advanced or metastatic disease) are important factors associated with the possibility to RTW [27]. For instance, ovarian cancer and lung cancer are usually diagnosed at later stage, thus treatment of such advanced disease with curative intent is consequently less likely, and also the possibility of employees, with such a diagnosis, to resume work [28]. In contrast, patients with breast cancer or testicular cancer have a fairly good prognosis, hence, employees diagnosed with these tumor types are frequently able to RTW and continue working after treatment [29].

Furthermore, it is well known that treatment modalities, e.g., surgery, chemotherapy and hormonal treatment, may directly influence RTW and continuation of work in cancer patients and survivors. In a study by Eaker et al. [30], breast

cancer patients on hormone treatment were at risk for prolonged sickness absence (Odds Ratio [OR] 1.3, 95% CI 1.1–1.5) [30]. Also, systemic treatments, such as chemotherapy and hormonal therapy, can be related to side-effects, such as fatigue, sleeping disorders, poor appetite, nausea and/or pain, and related problems, such as distress, depression, or anxiety, that can remain present for a long time, even after treatment is completed [31].

As expected, many studies have indicated that high levels of these symptoms are related to the ability to work [32–34]. In addition, surgery may also negatively influence the ability to work. For example, the use of a more invasive surgical technique in colon cancer patients is associated with a longer period of recovery and later RTW, i.e., 71 (14–252) days for open surgery versus 44 (6–84) days for laparoscopic surgery ($p < 0.05$) [27]. Furthermore, side effects of surgery may impede RTW as well. That is, it can introduce physical limitations, e.g., due to lymphedema, may hinder social functioning, e.g., in communication/speech, due to tracheostomy [33], or require workplace accommodations, because of stoma care, due to a colectomy.

Many studies have explored the relationship between cognitive impairment and RTW in cancer survivors. While a systematic review found no effect of impaired cognitive functioning and RTW, a negative effect on performance in work, e.g., impairments in memory, attention and concentration or speed op processing due to deteriorated cognitive functioning, was noted [35]. Considering these results, job demands that require optimal cognitive functioning, such as enduring concentration, can present a challenge in cancer survivors who are about to RTW or are already occupationally active.

Lastly, radiotherapy can also introduce problems among cancer survivors. For example, if applied to the head and neck region, radiation can affect swallowing and speech, which might interfere with certain work-related tasks such as having, lunch at work or communicating with colleagues [36].

12.5 Work-related Factors

When considering vocational rehabilitation in cancer survivors, several work-related factors can play a role. Sometimes job demands are hard to overcome. For example, physical strain and heavy lifting in the work place were found to be negatively associated with RTW in breast cancer survivors at 10 months sick leave (OR 0.1, 95% CI 0.0–0.8) [37]. In addition, Steiner et al. [38] reported that cancer survivors often needed to adapt their working role, including a reduction in working hours, when confronted with symptoms such as feeling depressed [38].

Additionally, the way a work environment is organized, the level of employer and co-worker support, as well as the support provided by occupational health services appear to be related to RTW outcomes [39]. Verbeek et al. [40] found that cancer survivors, who received a less personal approach from occupational health services had a prolonged time to RTW (HR 0.5, 95% CI 0.3–0.8) [40]. On the contrary, a positive attitude by employers towards cancer survivors' trajectories of vocational rehabilitation were positively associated with RTW at 12 months sick leave (OR 1.9, 95% CI 1.4–2.6) [34]. Finally, Pryce et al. [41] reported that cancer survivors' disclosure to colleagues of experienced health and work-related problems was found to be positively associated with the likelihood to continue work during treatment (OR 3.03, 95% CI 1.28–8.19) [41].

12.6 Factors Related to the Cancer Survivor and Reactions of Others

Socio-demographics, such as age, gender and education, and their association with work-related outcomes, were studied [13, 23, 24]. To date, findings regarding the influence of older age on RTW are inconclusive. For example, in prostate cancer survivors, an earlier RTW was found as age increased [42], but an opposite trend, i.e., a later RTW as age increased, was reported in a

study of colorectal cancer [43] and in a study addressing multiple cancer sites [32]. Findings may be influenced however by treatment options, as in the case of prostate cancer in which older age groups often do not receive as aggressive treatment [44]. Researchers found strong evidence for the positive association between older age at diagnosis and unemployment [45]. Moreover, moderate evidence revealed women having a reduced likelihood to RTW compared to men. For example, in a study on multiple cancer sites, Park et al. [46] found that female employees compared to men, were at greater risk to lose their job (HR 1.6, 95% CI 1.4–1.8) and needed longer time for re-employment (HR 0.6, 95% CI 0.4–0.8) [46]. With regard to educational level despite some mixed findings mentioned above, strong evidence found in several studies for lower education negatively associated with employment [45, 47].

A serious disease like cancer may change a person's perspective related to all aspects of life, including the meaning of work [48, 49]. For example, in a case of cancer types with poor prognoses, survivors may judge work as less important and focus on other alternative activities, e.g., related to daily family life or social activities [50]. The changed meaning of work may act as a barrier in the RTW process [16]. In addition, the way in which employees with a history of cancer cope with their disease is important. Previous studies reported that those applying mainly passive or avoidant coping strategies have more problems regarding RTW or staying at work compared to those with active, problem-solving coping strategies [51, 52]. On the other hand, a partner or spouse positively supporting a cancer survivor to resume former work-related tasks may in turn facilitate RTW and the same applies to support provided by other stakeholders [53, 54] including their health care providers. A study of cancer survivors on long-term sick leave, found that if a general practitioner or a clinical specialist has positive expectations related to RTW, a cancer survivor has a greater chance to actually work [55]. Finally, the way society judges work or absence from work, due to disease, can influence RTW in cancer survivors such that comparing countries, differences in social insurance systems which were reported to be associated with different RTW outcomes depending on, e.g., the maximum period of sick leave absence or compensation a worker on sick leave is entitled to [56–58].

12.7 Evidence Based Approaches for Managing RTW

In the last decade, a number of interventions and programs were constructed and their effects on RTW were evaluated. To understand the state of the science in this area, a comprehensive Cochrane systematic review and meta-analysis of the literature was conducted (de Boer et al. [9]) to evaluate the effectiveness of interventions aimed at enhancing RTW in cancer patients compared to alternative programs including usual care or no intervention [9]. The following electronic databases were examined: Cochrane Central Register of Controlled Trails, MEDLINE, EMBASE, CINAHL, OSH-ROM and OSH Update, PsycINFO, DARE, ClinicalTrails.gov, Trailregister.nl and controlled-trials.com. Inclusion criteria included randomized controlled trials of the effectiveness of psycho-educational, vocational, physical, medical or multidisciplinary interventions from 1990 to March 25, 2014. This comprehensive review of the literature yielded 15 separate randomized controlled trials, including 1835 cancer patients that met the inclusion criteria. The review showed that the 15 interventional trials were conducted mostly in affluent countries, including the United States ($n = 5$), UK ($n = 3$), Sweden ($n = 2$), the Netherlands ($n = 2$), Germany ($n = 2$) and Australia ($n = 1$). Also, most of the interventional research was conducted with breast cancer survivors ($n = 7$) [59–65] while the remaining studies included patients with prostate cancer ($n = 2$) [66, 67] and one study each for thyroid [68], gynaecological patients [69], head and neck cancer [70], laryngeal cancer [71], leukaemia [72], and mixed cancer diagnoses [73]. There were four separate types of interventional studies found including (1) psycho-educational interventions ($n = 2$); (2) physical intervention

(n = 1); (3) medical interventions (n = 7); and (4) multidisciplinary interventions, which were a combination of psycho-educational, vocational, and physical interventions (n = 5). No studies were found that focused only on vocational training. Overall, the review found four types of interventions including psycho-educational, physical, medical and multidisciplinary interventions. We describe the interventions from this review and the most recent updates to the science below.

12.7.1 Educational Interventions

Psycho-educational interventions included interventions aimed at providing information and support for cancer survivors. Lepore and colleagues [66] conducted a 3-arm trial including patient education alone, patient education combined with group discussions to improve coping and usual care in 124 prostate cancer survivors [66]. Purcell et al. [73] provided education on reducing fatigue for patients receiving radiotherapy with three comparison groups, including post-radiotherapy fatigue education (n = 43), pre- and post-radiotherapy fatigue education (n = 23) and controls receiving a one-page flyer with generic information on fatigue (n = 72) [73]. In summarizing these interventions that included 260 patients with 148 in the intervention group compared to 112 patients in the control group, there were no considerable differences in effect on RTW or quality of life between groups [9].

12.7.2 Physical Activity Interventions

At the time of the Cochrane Review, one small intervention focused on a physical intervention aimed at enhancing RTW. Rogers et al. [64] conducted a small RCT that included an individually supervised exercise session, individualized counselling with an exercise specialist, and home-based exercises (n = 14) compared to usual care (n = 14). There was no significant difference between the intervention group compared to control in RTW or quality of life.

12.7.3 Medical Interventions

Cancer treatment alternatives may also be a factor in RTW. Seven studies examined the effects of a less intense medical intervention versus a more intense and radical medical intervention on RTW [61, 62, 68–72]. Medical interventions were diverse including intra-atrial chemo-radiation [70], thyroid-stimulating hormones administered after surgery [68], chemotherapy [71], adjuvant endocrine therapy [61], laparoscopy [69], breast conservation [62], and peripheral blood progenitor cell transplantation [72]. Although some individual studies identified that less intense medical treatment resulted in earlier RTW [69], when the studies were pooled in the meta-analysis evidence showed that less intense treatments resulted in similar RTW rates as more intense, radical treatments [9].

12.7.4 Multidisciplinary Interventions

We identified five RCTs that examined the effect of multidisciplinary interventions on RTW. These studies included vocational counselling, physical training, or both, in combination with patient education or counselling or both [59, 60, 63, 65, 67]. Individual studies and pooled analysis, in the meta-analysis, noted that multidisciplinary interventions led to higher RTW rates than usual care [9]. Overall, only studies that included vocational counselling combined with patient education, patient counselling, and biofeedback-assisted behavioural training or physical interventions were effective in improving RTW. It should be noted that all but one of these studies were conducted in breast cancer and thus, the long-term and late effects of specific cancers and their treatments may differ and play a role in work outcomes such as RTW.

12.8 More Recent Studies

Since this review was published in 2015, three additional noteworthy trials were identified that explored physical and multidisciplinary

interventions. Van Waart et al. [74] examined the effectiveness of a low-intensity, home-based physical activity program (Onco-Move) and a moderate to high-intensity, combined supervised resistance and aerobic exercise program (OnTrack) versus usual care (UC) in maintaining or enhancing physical fitness, minimizing fatigue, enhancing health-related quality of life, and RTW. Outcomes of this trial were positive with the intervention groups reporting significantly higher RTW rates than the usual care (83% and 79% versus 61%, $p = 0.012$) and worked a significantly higher percentage of pre-illness hours on the job than the usual care group (59% and 60% versus 42%; $p = 0.014$) [74].

Van Egmond and colleagues [14] conducted a RCT to assess the effect of a tailored return to work program in cancer patients with job loss [14]. This RCT sought to compare an individualized re-integration plan and development of a consensus-based return to work plan with coaching sessions to usual care on sustainable RTW in 171 cancer survivors with diverse diagnoses. Although, some improvement in duration until sustainable RTW was noted in the intervention group compared to control, these results were not statistically significant. The authors suggest that results may have been influenced by the cancer survivors original employment status; because unlike most studies to date these cancer survivors did not have a stable employer to return to, and thus, did not benefit from employer-related factors, such as work accommodations and support from the workplace, which are strongly associated with positive work outcomes [75].

Most recently, Leensen and colleagues [76] conducted a carefully designed feasibility trial to evaluate a multidisciplinary intervention combining occupational counselling with physical exercise to enhance cancer patients' RTW [76]. This study also assessed whether care providers and patients were satisfied with the intervention and whether it was performed in such a way that the cancer survivor thoroughly understood the barriers and facilitators related to implementation of this intervention. This feasibility trial examined reach, dose delivered, dose received, fidelity, patient satisfaction, feasibility and perceived usefulness according to health care providers and communication among providers. The study, which placed a significant emphasis on quality design and delivery, demonstrated successful delivery and receipt of over 75% on all intervention components. Key factors of patient motivation facilitated intervention participation and uptake, while physical limitations hindered the exercise component of the intervention. This study lays the groundwork for a larger multidisciplinary intervention trial to be incorporated with the care of newly diagnosed cancer survivors to promote RTW.

Additional reliable and valid instruments are readily available. The World Health Organization (WHO) Health and Work Performance Questionnaire is widely used to measure four aspects of work functioning including: absenteeism, performance while at work, work-related accidents and job turnover (available at http://www.hcp.med.harvard.edu/hpq) [77]. For more information, Prasad and colleagues [78] provide a comprehensive review of self-reported instruments focusing on health-related work productivity [78]. Examining the economic impact of cancer on work outcomes will be a key area for future research.

To conclude, intervention programs that involve a multidisciplinary approach with psycho-educational physical, vocational components were most successful in improving RTW. However, it is unclear in these bundled interventions the specific active components of these types of interventions are currently unknown. In addition, studies to date have not focused on vocational counselling and incorporation of the employer as a partner in RTW or work retention. It is important to explicitly emphasize that future research will need to not only examine RTW but also identify effective interventions for work absenteeism, work productivity and performance upon return to work.

12.9 Other Approaches and Interventions for Managing Work-Related Concerns

In the above-mentioned Cochrane systematic review and meta-analyses, only RTW interventions were included which had been evaluated within an RCT. However, RCTs are sometimes difficult to execute in various types of work environments. Several other interventions and programs to support RTW in employees with a cancer diagnosis have been developed and implemented, but were not evaluated using RCTs. Most of those interventions were developed for cancer survivors. Some interventions especially involved employers, human resource professionals, line managers, or health care professionals. Only a few interventions were available for small and medium-sized enterprise owners (SMEs) and the self-employed affected by cancer (e.g. http://www.macmillan.org.uk/information-and-support/organising/work-and-cancer/if-youre-an-employer/index.html#161443, Dutch Organization of Cancer Patient Organizations, https://www.kanker.nl/bibliotheek/werk/blijven-werken-en-werkhervatting/2084-starten-als-ondernemer; Re-turn (www.return.nl), Breastcancer.org, http://www.breastcancer.org/tips/your_job/self_employed and Kobra-Berlin (DE) https://kobra-berlin.de/nc/workshops-veranstaltungen/event/133.html. As mentioned earlier the focus over the next decade should be on the design and execution of well-controlled intervention studies that consider the involvement of key stakeholders, different types of work environments or settings and various work outcomes.

12.9.1 Cancer Survivors

Cancer survivors can receive support from their employers in the RTW process. For example, the company has RTW programs and policies in place that can assist cancer survivors with workplace concerns [79, 80]. These programs and policies include workplace adjustments and accommodations such as the adjustment to working hours (e.g., gradual RTW, flexible working hours, zero-hour contracts), adjustments in the workplace (e.g., own office space instead of open-plan office, remote work), paid leave for health care appointments, and adjustments to the workload (e.g., job-sharing, reduced demands, provision of assistance) [50, 81–83].

In certain countries, cancer survivors can find further support from non-governmental organizations (NGOs). These services are mostly informative (resources) and do not include rehabilitation. The aim of these interventions is to enable cancer survivors to adapt to their new situations and make informed decisions regarding their RTW. The information is disseminated in printed form (e.g., brochures), personally (e.g., in-house counselling, telephone), or on the internet (e.g., online articles, videos, and webinars) [84].

Finally, a potentially useful work-related guidance tool is available for those diagnosed with cancer that enables them to take the lead in stimulating discussion with a range of different healthcare professionals, employers, employment agencies and support services. The tool facilitates discussions through a set of questions that individuals can utilise to find solutions and minimize the impact cancer diagnosis, prognosis and treatment may have on their employment, sick leave and return to work outcomes [85].

12.9.2 Employers

Support for employer's focuses on managing ill workers and how to support their RTW, e.g., what are appropriate workplace accommodations? The interventions available for employers are mainly informative, and can also include counselling or in-house training courses. Scientific evaluation on the effectiveness of available interventions is lacking [39].

Interventions and resources currently exist for employers, line managers, and human resource professionals in the form of personal consultations, videos, newsletters, webinars, posters, booklets, workshops, and e-learning courses. They are available, for example, via the UK

Macmillan Cancer Support organizations [86] and the US Job Accommodation Network [87]. Topics covered in the various programs and resources for employers typically include general information about cancer, legislation and finances, roles, and the support needs of staff and cancer carers. Information is available on how cancer and its treatment affect people and how this may affect a person's work. Employers can learn about common myths and facts, and about death and bereavement. Further information is available on the legal background related (country specific) to work and cancer, the financial support available to workers, the role of the employer and occupational health, and the support needs of staff and working caregivers.

Other topics in this material include communication with survivors and their colleagues or how to practically support cancer survivors' RTW and remaining at work. The employer can learn about confidentiality issues, managing absences, workplace policies, creating a RTW plan, and possible changes to work arrangements (workplace accommodation/adjustments). Possible workplace accommodations are, for example, paid working time for medical appointments, reduced working hours, and RTW meetings. While these resources do provide information found anecdotally useful we must emphasize that while this type of information have been made available for years for other illnesses the careful evaluation of such information and their addition to other interventions for cancer survivors either who need to RTW or are at work must be carefully evaluated to identify the most effective and efficient approaches to work re-entry and sustainability among cancer survivors.

12.9.3 Health Care Professionals

Various types of health care professionals (e.g., medical oncologists, primary care providers, advance practice nurses, social workers, psychologists, physical therapists and occupational therapists) can support cancer survivors' RTW. Interventions to improve health care professionals' skills and expertise may include information advising on how to communicate about employment issues with people affected by cancer, how to develop and deliver care and services, and information on their respective roles and responsibilities [88].

Guidelines that provide advice on, for example, workplace accommodations, or communication between health care professionals or with cancer survivors are available. For example, in a Dutch study, participants were given support on how to communicate about the cancer diagnosis, the treatment plan and its outcome. Cancer survivors and physicians also received an additional leaflet that described a detailed 10-step plan for returning to work, which included an activity plan and goals [89]. In this feasibility study, 24 survivors and 26 occupational physicians who participated in the study found the program useful (i.e., 7 on a 0–10 scale) and adhered to the majority of recommendations (7 out of 10 guidelines). Although these results are encouraging, there was no effect on actual return to work in this small sample. More work is needed to test and refine guidelines to support cancer survivors RTW.

12.9.4 Small and Medium-Sized Enterprise (SMEs) Owners and Self-Employed

Interventions that specifically focus on small and medium-sized enterprise owners and the self-employed are rarely described in the literature, and are likely to be unavailable. This is despite the fact that SMEs are by far the biggest proportion of enterprises. Interventions that are currently available are via telephone, video, or in written form.

Interventions that are especially for the self-employed cover topics about treatment decisions and about founding, running, and closing down a business. This includes information about working during treatment, giving up work, managing workload, making decisions about working, financial issues and support, and communication with clients [90].

Owners of SMEs have access to relevant information that includes legal responsibilities, communication, examples of support for carers and survivors, and the impact of cancer on their business (e.g., via MacMillan in the UK [86] or Breast Cancer organization in the US [91].

12.10 Changes in Global Policies

Many people, who were diagnosed, received treatment for cancer or recovery from treatment, are employed and can continue to make valuable contributions to their employers. However, discrimination as it relates to employment is a concern for cancer survivors [92]. Legislation to protect individuals with disabilities and support RTW are important for cancer survivors.

In the United States, the American disabilities Act (ADA) was the first civil rights law to address concerns related to disability. The law introduced in 1993, prohibited discrimination of the disabled in employment, public services, public accommodations, and telecommunications [93]. Concerns arose as the definition of disability was found to exclude protection of individuals with cancer, diabetes and epilepsy. Therefore in 2008, the ADA Amendment Act was enacted and the definition of disability was broadened to include protection to those individuals [94]. Under the laws, employers with 15 or more employees are required to make provisions for the disabled to participate in the job application process and provide reasonable accommodations in the workplace. Modification to the work environment or a job that facilitates their ability to perform necessary job related tasks, can include tangible items, such as a piece of equipment or intangible such as an adjusted work schedule [94].

In 1993, the Family Leave Medical Act (FMLA) was introduced to address the lack of employment policies to protect working individuals from discrimination when needing to participate in early childbearing, or the care of personal or family members with serious health conditions. The act stipulated that the employer must allow the employee to return to the same job or provide an equivalent position. The employer is required to continue to provide employee benefits, such as insurance and accrual of seniority and benefits and opportunities for advancement upon return [95].

In Canada, health care resources are largely directed towards the provinces and each determines the priority services they will provide [96]. Employment insurance is a short-term sick leave plan lasting 15 weeks. It is available to individuals whose earnings dropped more than 40%. The Canadian Pension Plan is designed to meet the long-term needs of those whose disability are identified as both severe and prolonged and precludes them from performing the tasks in any job. However, receipt of the Canada Pension Plan Disability Program is dependent on the individual paying into the program for at least 25 years, and as a result is not always available to all cancer patients [97]. The Ontario Human Rights Commission developed and implemented the Ontario Human Rights Code to ensure that persons with disabilities are not discriminated against or harassed in the workplace; and that they have an equal right to employment. The code stipulates accommodations for RTW exists only if the employee can fulfil the required job expectations, if they cannot fulfil the requirements despite the accommodations; they are not guaranteed the right to RTW [97].

In the United Kingdom, the Equality Act (2010) was enacted to protect individuals from discrimination in the workplace and in society. This act made laws around disability easier to understand. It also strengthened protection for patients with cancer, as eligibility for disability is considered on the day of cancer diagnosis. Among European countries, the European Cancer Bill of Rights was introduced to address the disparities in equitable access and optimal standard of care for patients with cancer [98]. While this bill does not specifically address disability, it does define quality standards for access to care and the delivery of information and cancer care for European citizens [98].

In most countries, when an individual is receiving disability benefits, they are not allowed to work, however, according to the Organisation

for Economic Co-operation and Development (2010), some European countries have programs that allow employees to work part-time, while still receiving disability benefits. This is beneficial because it raises the financial income and can offset financial incentives of not returning to work. Further, it dispels the idea that disability benefits are permanent, and it promotes a relationship with the employer and the workplace, therefore promoting feelings of productivity while recovering from illness [99].

While progress was achieved in facilitating the RTW for cancer survivors, a gap exists for those who have the need for a convalescence period greater than 12 weeks (United States) or 15 weeks (Canada), but do not require permanent disability. Mehnert et al. [13] found cancer survivors returned to work after an average of 151 days being absent from work. This is 46 days longer than what is allotted by the maximum time of 15 weeks in Canada given to cancer survivors. More research is needed to develop vocational and physical rehabilitation guidelines that address these complex needs for employed cancer survivors to facilitate successful RTW.

12.11 Future Directions

Much progress has been made over the past 40 years regarding work and cancer survivorship. Table 12.1 displays a short list of tools that have been used to assess work-related outcomes in cancer survivors. Attention has shifted from focusing solely on job discrimination to efforts to not only identify risk factors, but also to develop evidence-based interventions to promote work reintegration as well to work sustainability. It is without question that cancer survivors place significant value on RTW. Cancer survivors identify work as a priority to regaining a 'sense of normalcy' not to mention the impact on their financial and social situations.

Research identified that disease-related factors, along with work-related factors, person-related and environmental factors, may play a significant role in RTW and other related-work outcomes. Advancements in early detection and improved treatment options have led to increased survival and, in turn, the need to focus on the longer-term treatment effects on RTW. Efforts, primarily over the last 10–15 years, were made to not only identify factors that influence RTW, but also to identify interventions that may lead to a smooth re-introduction to work. Multidisciplinary interventions, which include vocational counselling, show promise in the RCTs.

However, research in the area of cancer and work has predominantly focused on a select population of cancer survivors, namely those who are employed by others, and those with breast or colorectal cancers. While the narrow focus provided much needed insight into the issues affecting employed cancer survivors, more attention should be given to the work situation of specific groups of cancer survivors (e.g., colon, hematologic malignancies) and demographic groups (e.g., younger cancer survivors, survivors of childhood cancers, and ethnically diverse survivors) [104–106] and employee types (i.e., those unemployed at time of diagnosis seeking employment after treatment, the self-employed and those working in small organizations), since the number of all survivors are expected to increase in the future.

While there are a growing number of RTW intervention studies conducted with cancer survivors, these predominantly focused on health care-led interventions. There needs to be more involvement of employers in RTW interventions, as employers are drivers for implementing work adjustments and in providing support to a cancer survivor. It is these factors that may inevitably affect a timely RTW. Therefore, more workplace-focused interventions that involve both healthcare and the employer are required. Overall, well-designed RTW and workplace intervention studies are needed that report reach, dose delivered and received, fidelity, feasibility and usefulness according to the cancer survivor, and employer and not just by those delivering the intervention.

Current research predominantly focuses on RTW outcomes and more research is required on work sustainability. For example, identifying what factors and characteristics enable cancer survivors to not only RTW, but to remain productive and active in the labour market until they are ready to

Table 12.1 Work-related outcome questionnaires

Variable	Measure	# Items	Potential score range (total)	Subscales item #/ range	Reliability range*	Meaning of the results
Self-focused emotional labor	Emotional labor scale [100]	6	6–30	n/a	0.77–0.83	Higher scores indicate more emotional labor
Work well-being	Utrecht work engagement scale [101]	17	0–6 Global = average of all items	1. Vigor (items 1, 4, 8, 12, 15, 17) range = 0–6 2. Dedication (items 2, 5, 7, 10, 13) range = 0–6 3. Absorption (items 3, 6, 9, 11, 14, 16) range = 0–6 Domain scores are average of item scores	0.93 (single domain) Vigor: 0.82; dedication: 0.89; absorption: 0.83 (3-domain)	Higher scores suggest better work well-being. Depending on the needs of the study, scale can be used as single or 3-domain
Work productivity and performance	Work limitations questionnaire (WLQ) [102]	25	25–125 Item range 1–5	1. Time management: (items 1a–1e) range = 5–25 2. Physical scale (items 2a–2f) range = 6–30 3. Mental-interpersonal scale: (items 3a -4c) range = 9–45 4. Output scale: (items 5a–5e) range = 5–25	0.84, 0.79, 0.92 and 0.92, respectively	Higher scores are indicative of poorer work performance, except for the physical demands sub-scale in which higher scores indicate better work performance
Work ability	Work ability index (WAI) [103]	7	7–49	WAI total score = range 7–49	0.82	WAI total cut score ranges: 7–27 = Poor 28–36 = Moderate 37–43 = Good 44–49 = Excellent

retire. A key challenge is involving not just cancer survivors, but also their employers to help define some of the problems around keeping cancer survivors at work and to identify possible solutions.

Due to the combined effects of ageing of the working population and later retirement age, the incidence of cancer in the working population will increase and more people will seek to RTW and sustain a working life as survival rates increase. These emerging issues require research in cancer and work to take a life course perspective that examines how a cancer diagnosis and its treatment and side effects impact work, and how work impacts recovery or exacerbates symptoms for different age groups and for different demographic and socio-economic situations.

Effective methods of data collection are required to study a life course perspective in cancer and work. There are only a few measures for assessing the balance between individuals' abilities and their tasks, which may be applied to studying people longitudinally, from point of diagnosis to transit into returning to work, to sustaining employment and to retirement and old age. While measures such as the Work Ability Index and the Work Limitations Questionnaire are important workplace measures, other measures are also required that examine the impact of

symptoms side-effects on psychological well-being and coping with work demands. Therefore, researchers need to work together across disciplinary teams, when examining the effects of cancer that extend beyond retirement into old age. This approach requires using big data (i.e., an emerging and rapidly growing area of research method that obtains and combines a range of datasets to examine the relationships between cancer diagnosis, treatment and interventions, employment factors and long-term work ability).

Finally, more translational research is needed to support reintegration of cancer survivors in the workforce. Health care providers must seek to identify survivor's goals in regards to RTW and assist them and their family to achieve these goals. Individualized survivor care plans should be developed and include work-related goals to support a smooth transition back into the workforce. We need to understand the essential components of these interventions requisite for meaningful positive outcomes, as well as, trials that include a more diverse cancer population. In addition, advocates need to continue to emphasize the need for legislation to support cancer survivors in their efforts to RTW and remain as active members in society.

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Sleep

13

Marie-Hélène Savard and Josée Savard

13.1 Introduction

Once a neglected problem, research conducted on cancer-related sleep has proliferated in recent years. In fact, PubMed entries for "cancer" and "sleep" have more than tripled in the last decade. This chapter focuses on the prevalence, screening, assessment, and pharmacological and non-pharmacological treatment of sleep difficulties in cancer patients and cancer survivors, with an emphasis on the knowledge accumulated in recent years.

13.2 Prevalence and Evolution of Sleep Disturbances

Sleep disturbances are amongst the most prevalent problems in patients with cancer [1, 2]. Up to a quarter of cancer patients use a hypnotic medication, often for years [3], which also reflects the high prevalence and persistence of sleep problems in this population. While insomnia is the main sleep complaint of cancer patients and survivors, and is the focus of this chapter, they may also suffer from other sleep disorders including hypersomnolence and obstructive sleep apnea, or a combination of these.

13.2.1 Cross-sectional and Longitudinal Studies of Subjectively Assessed Sleep

Non-metastatic Cancer Reviews of early cross-sectional studies reported rates of sleep difficulties (such as difficulty falling or staying asleep, early morning awakenings, or non-restorative sleep) varying from 30% to 50% in cancer survivors with mixed cancer diagnoses [4–11]. Most of these studies conducted sleep assessments several months and even years following completion of treatment for cancer, hence the prevalence and evolution of sleep difficulties throughout and after the treatment phase was unknown. Also, the use of small, convenience samples and the use of sleep measures composed of single item or a small number of items and not validated assessment tools limit conclusions drawn from these studies.

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More recent longitudinal studies have provided information on the prevalence, incidence, remission and persistence of sleep complaints throughout the cancer care trajectory and beyond. Our research team followed 991 patients with heterogeneous cancer types from the peri-operative period to 18 months later [12, 13]. At baseline, 59% had insomnia symptoms, including 28% with an insomnia syndrome, as assessed using a diagnostic interview administered over the phone [14] and an adaptation of the diagnostic algorithm developed by Morin and his colleagues [15]. Accordingly, patients were considered to have an insomnia syndrome when they met the following criteria: sleep-onset latency (SOL) or wake after sleep onset (WASO) >30 min, at least 3 nights per week, sleep efficiency (SE); (total sleep time/total time spent in bed) < 85%, for at least 1 month, impaired daytime functioning or marked distress OR using a hypnotic medication 3 nights/week or more for at least 1 month. Although these rates decreased over time, a third of the sample (36%) continued to report insomnia symptoms at the 18-month evaluation, of which 21% met the criteria for an insomnia syndrome. This remains much higher than in the general population with a prevalence of insomnia syndrome estimated at 9–12% [16–18]. Moreover, the general persistence rate (i.e., presence of insomnia on two consecutive time points on 2–4 month intervals) was 51%, while 35% of patients had insomnia persisting over at least three consecutive time points (up to 8 months). The insomnia syndrome was a particularly enduring condition with persistence rates varying from 69% to 80%.

Palesh et al. conducted another large-scale prospective study [19] among 823 patients scheduled to receive at least 4 cycles of chemotherapy for various types of cancer (all stages). Sleep difficulties were assessed on day 7 of cycle 1 and 2 of chemotherapy, using the six sleep-related questions from the *Hamilton Depression Inventory*. After their first chemotherapy cycle, 80% of the participants reported insomnia symptoms, including the 43% meeting the authors' criteria for an insomnia disorder as defined by the presence of difficulty falling asleep, difficulty staying asleep and/or early morning awakenings (at least 30 min each) for at least 3 nights a week for 2 weeks. These rates decreased to 68% and 35%, respectively, at the second chemotherapy cycle. Among good sleepers at cycle 1, 35% developed insomnia symptoms at cycle 2 (of whom 10% developed an insomnia disorder). There was no measure taken post-chemotherapy.

Cancer Type Available evidence indicates that the prevalence of sleep disturbances varies as a function of cancer sites. In the longitudinal study of Palesh et al. [19] the prevalence of insomnia symptoms was the highest in breast (85%) and gynaecological cancer (83%), although the rates were elevated in other types of cancer as well (e.g., haematological [81%], lung [80%], and gastro-intestinal [64%]). The prevalence of the insomnia disorder was the greatest in patients with lung cancer (51%) and the lowest in those with a gastro-intestinal malignancy (24%). Savard et al. also found the highest rates of insomnia symptoms in breast (42–69%) and gynaecological (33–68%) cancer patients, whereas the lowest rates were obtained in men with prostate cancer (25–39%), throughout the 18-month study [12]. It is of note, however, that no patients had lung or hematological cancer (only patients receiving surgery were included) in this study and that those with other types of cancer were insufficiently represented in the sample to be compared.

Advanced Cancer Sleep difficulties appear to be even more common in patients with advanced cancer. From about half to three-quarters of outpatients attending cancer or palliative care clinics report some sleep disturbance [20–25]. Wide ranges of sleep complaints are typically reported. A study conducted by our research team in patients receiving palliative care and with an ECOG of 2 or 3 revealed that 68.6% of the sample had at least one type of sleep-wake difficulty (disorder or symptoms): 31.4% had insomnia and 29.4% had hypersomnolence as their main sleep-wake problem and 25.6% had a combination of sleep difficulties [26]. Hence, both nocturnal and daytime sleep and vigilance can be affected in advanced cancer.

Having a poorer performance status (Karnofsky or ECOG score) is associated with increased sleep-wake disturbances [25]. As such, a very high rate of sleep difficulties (96%) was observed among 82 advanced cancer patients referred to a palliative care unit for control of pain and other symptoms [27]. Pain, fatigue, depressive symptoms, and usage of sedative medications are significantly associated with sleep difficulties in this population [22, 23, 28]. Importantly, one study suggested that poor sleep quality and use of sleep medications were, along with hopelessness and depression, the best predictors of desire for hastened death in 102 terminally ill patients attending a palliative care unit [29]. This relationship argues even further for the importance of offering appropriate sleep management to these patients in order to improve their quality of life. Based on results obtained by our research team [26], particular attention should be given to distinguishing hypersomnolence vs. insomnia disorders, as these require different types of interventions. It is also important to identify other risk factors for sleep disorders specific to this population such as opioid medication, circadian disruptions, and environmental factors in both ambulatory patients and those in the hospital setting (e.g., light exposure, noise).

13.2.2 Polysomnography, Actigraphy, and Circadian Rhythm Recording

As in the general population, polysomnography is seldom used for the clinical assessment of sleep disturbances among cancer patients. Some studies found significantly more sleep alterations (e.g., lower SE and higher WASO) in lung or advanced cancer patients as compared to individuals with no cancer [30, 31]. In contrast, the sleep architecture (e.g., SOL, WASO, total sleep time) of 56 breast cancer patients (stage I-III) who underwent home-based polysomnography was found to be similar to normative data of women with no cancer in the same age group [32]. These discrepancies point to the need to further investigate objectively recorded sleep according to type and stage of cancer to better understand how sleep is impaired in various patient subgroups. Also, we propose that the assessment of more fine-grained EEG parameters, such as spectral analysis or cyclic alternating pattern, may potentially reveal certain sleep alterations (e.g., increased beta-wave frequency) that are not identified using conventional sleep-stage scoring.

Actigraphy is another objective measure that can provide information on sleep, more specifically indicators of the rest-activity cycles over 24-h periods. Studies using actigraphy among cancer patients have consistently found less contrast between daytime and nighttime activity in these individuals as compared with controls, which is indicative of circadian disruption [33–35]. This finding is of concern, given that less robust sleep-wake rhythms have been associated with increased depressive symptoms and poorer survival among cancer patients [36, 37]. Yet, such cross-sectional findings need to be interpreted cautiously as it could be the poorer prognosis that leads to impaired circadian rhythms.

Rest-activity cycles are particularly disrupted with chemotherapy. In a study conducted among 49 patients with advanced cancer, 45% displayed disrupted rest-activity patterns for several days following the administration of chemotherapy, characterized by increased nighttime activity and decreased diurnal activity [38]. This effect of chemotherapy on rest-activity rhythms appears to be cumulative over repeated treatments, as Savard et al. [39] showed. In this study, the rest-activity pattern of 85 women with stage I-III breast cancer was measured over 4 cycles of chemotherapy. Actigraphic measures were taken during 72 consecutive hours at baseline (pre-chemotherapy), as well as during week 1, 2, and 3 of cycle 1 and cycle 4 of chemotherapy. At the first administration of chemotherapy (week 1, cycle 1) a transient disruption of rest-activity rhythm was observed, with an almost complete return to baseline values at week 2 and 3. However, at cycle 4, sleep-wake rhythm impairments were sustained at week 2 and 3. There was no measure taken post-chemotherapy in that study.

Another prospective study conducted among 68 women, again with stage I-III breast cancer, confirmed these results in addition to reporting data beyond the treatment phase. Results indicated

increased rest-activity disruption after 4 cycles of chemotherapy as compared to baseline [35]. However, 1 year later, these patterns were back to pre-cancer treatment levels. Interestingly, the authors also observed that breast cancer patients had more disrupted sleep-wake cycles than matched controls even prior to chemotherapy. This suggests that other cancer-related factors (e.g., surgery) occurring earlier in the trajectory may contribute to these alterations [35].

Circadian disruptions that are present prior to the cancer diagnosis may be involved in carcinogenesis. Indeed, shift work and/or nighttime light exposure have been associated with a significant increase in the incidence of solid tumors, lymphomas and leukemia, and is now recognized as a probable carcinogen in humans by the International Agency for Research on Cancer [40, 41]. Animal models have also shown that the alteration of light environments and the disruption of genes generating circadian rhythms accelerate cancer progression relative to controls [40]. Recently, our team observed that a less rhythmic sleep-wake cycle and a lower 24-h light exposure was associated with a shorter time to death among a sample of 55 community-dwelling cancer patients receiving palliative care with an ECOG of 2 or 3 [42], which is in line with prior results [43–45]. Again caution is needed when interpreting such findings as they could suggest that impaired sleep-wake cycles predict a poorer prognosis or conversely that a poorer prognosis predicts more sleep-wake cycle impairments.

Overall, more research is needed, in particular longitudinal studies which include larger samples and individuals with other cancer types and stages, in order to better assess the evolution of rest-activity rhythms throughout various cancer care trajectories.

13.3 Etiology and Risk Factors of Insomnia in the Context of Cancer

Spielman's model [46], also known as the 3Ps model, which was initially developed to better understand the etiology of primary insomnia, is also very helpful to delineate the predisposing, precipitating, and perpetuating factors involved in the development of insomnia among cancer patients and survivors (see Table 13.1).

13.3.1 Predisposing Factors

Contrary to primary insomnia, insomnia comorbid with cancer is more prevalent in younger individuals [19, 25, 47, 48], who also generally display higher levels of psychological distress. A younger age is also associated with an increased likelihood for women to experience menopausal transition during cancer treatments due to their systemic effects on the reproductive system. This also can increase the risk for sleep impairments [49] (see Precipitating Factors section). The female sex and a hyperarousability trait have also been found to increase the risk for developing insomnia symptoms associated with cancer [13]. Personal and family antecedents of insomnia and other psychological disorders could also constitute a factor increasing one's vulnerability to sleep difficulties when cancer occurs.

13.3.2 Precipitating Factors

Insomnia is often triggered by a stressful event [50]. Several potential stressors may occur during the cancer diagnosis, treatment and survivorship phases and precipitate insomnia. This includes the diagnosis itself, the surgery and other cancer treatments received, the many impacts of cancer and its treatment on the patient's life, and the cancer's recurrence or progression to palliative and terminal stages of the disease.

Particularly high levels of sleep disturbances are observed during the period surrounding tumor removal surgery, which most commonly occurs shortly after the cancer diagnosis [12, 51]. Factors such as anticipatory anxiety and intrusive thoughts prior to the surgery can disturb sleep [52]. However, it is still unknown whether those sleep impairments are part of a pre-existing problem, and whether and how long they persist after surgery. Studies with extended follow-up are needed to answer these questions.

Table 13.1 Predisposing, precipitating, and perpetuating factors for insomnia comorbid with cancer

A. *Predisposing factors*
Younger age
Being a woman
Hyperarousability trait
Personal and family history of insomnia
Antecedents of a psychiatric disorder (e.g., depressive or anxiety disorders)
B. *Precipitating factors*
Psychological reaction (e.g., depressive/anxiety symptoms) to:
Initial diagnosis
Recurrence diagnosis
Progression
Cancer treatments
Surgery
Psychological reaction
Hospitalization (e.g., environment, changes in sleep routine)
Side effects (e.g., pain, nocturia)
Chemotherapy
Side effects (e.g., nausea/vomiting, fatigue)
Medications used (e.g., antiemetics)
Deficiency in sexual hormones (e.g., nocturnal hot flashes)
Changes in circadian rhythms
Hormone therapy
Deficiency in sexual hormones (e.g., nocturnal hot flashes)
Side effects (e.g., pain)
Radiation therapy
Side effects (e.g., fatigue, nocturia, pain)
Changes in circadian rhythms
Cancer symptoms (e.g., pain, dyspnea)
Delirium
C. *Perpetuating factors*
Maladaptive sleep behaviours
Excessive amount of time spent in bed
Irregular sleep-wake schedule
Napping
Engaging in sleep-interfering activities in the bedroom
Faulty beliefs and attitudes about sleep
Unrealistic sleep requirement expectations
Faulty causal attributions
Misattribution/amplification of perceived consequences of insomnia (e.g., on cancer progression)
Decreased perception of control/predictability of sleep
Faulty beliefs about sleep-promoting practices

Adapted from Savard and Savard [164]

Hospitalization in general can also trigger sleep disturbances [53]. Light (too much in the evening and too little during the day), noise, bed discomfort, or interventions during sleeping periods are all environmental factors that may prevent continuous sleep during a hospital stay, but anxiety and behavioural factors such as modification of the sleep routine may also come into play. Hopefully, as outpatient surgeries are increasingly being performed in cancer, this will reduce the importance of hospitalization as a contributing factor to sleep disturbances.

Side effects of surgery, which may persist months and even years after, such as nocturia (e.g., following radical prostatectomy) and pain can also trigger sleep disturbances. In particular, there is a clear bidirectional relationship between sleep impairments and pain [54]. Overall, although this hypothesis warrants investigation, it would appear that the perioperative period is the starting point of many insomnia cases which are likely to persist during the cancer care trajectory [12].

Other cancer treatments may exert a detrimental effect on sleep, either directly (e.g., physiological) or indirectly (e.g., side effects, emotional impact). As stated above, chemotherapy is thought to cause significant circadian sleep-wake rhythm disruption, and insomnia symptoms are common prior, during, and after chemotherapy [19, 51, 55, 56]. Hormone therapy for cancer (e.g., tamoxifen, goserelin) appears to be another important precipitating factor of insomnia [25, 57]. In particular, the deficiency in sexual hormones (estrogen in women, testosterone in men) induced by this type of treatment can trigger insomnia through the occurrence of hot flashes, a significant contributor to sleep impairments [32, 49]. It is of note that this abrupt hormone deficiency is also observed following chemotherapy and orchiectomy. In addition, the sudden cessation of hormone replacement therapy in women, which is often recommended following a breast or gynecological cancer diagnosis, may also induce or exacerbate nocturnal hot flashes [58], thus interfering with sleep. Finally, radiotherapy is also potentially harmful for sleep, but to a lesser extent [59].

Many cancer-related somatic symptoms occurring during treatment and often persisting throughout survivorship may impact sleep negatively. Pain, dyspnea, urinary symptoms (e.g., following radical prostatectomy or radiation ther-

apy in the urogenital area), or gastro-intestinal symptoms (e.g., chemotherapy-induced nausea), as well as the medications commonly administered to help prevent or relieve such symptoms, such as antiemetics (corticosteroids), or analgesics (opioids) all contribute to worsening sleep [60–63].

Pain as a side effect of surgery and other cancer treatments (e.g., aromatase inhibitors) is particularly liable to disturb sleep. A study conducted among 2862 cancer patients with various cancer types and treatment regimens found that individuals reporting clinically significant pain were 2.7 times more likely to experience sleep difficulties than those without pain [64]. This is consistent with other empirical evidence showing that pain significantly predicts the incidence or exacerbation of subjectively assessed sleep difficulties [65, 66]. One study also found that male patients in pain with prostate, brain or lung cancer had greater sleep disturbances on actigraphy and more rest-activity rhythm impairments than pain-free individuals [67].

With regard to fatigue, a symptom affecting nearly all cancer patients at some point [68], there is evidence that it is a significant risk factor of cancer-related insomnia, although it is most commonly perceived as a consequence [69]. Changes in patients' routine to cope with fatigue, such as increased napping and rest, and consequent reduced natural light exposure, may eventually alter circadian rhythms and make their nighttime sleep less consolidated and lighter [70–73].

13.3.3 Perpetuating Factors

According to Spielman's cognitive-behavioural framework of insomnia [46], the persistence of insomnia over time is mainly due to the development of maladaptive sleep behaviours and dysfunctional sleep-related cognitions in reaction to sleep difficulties. This conceptualization is also relevant for cancer-related insomnia. Indeed, although the persistence of some sleep-disturbing factors such as pain or hot flashes may contribute to perpetuating cancer-related sleep impairments to some extent, it is mostly the individuals' reaction to the sleep problem that will determine whether insomnia will remit or become chronic. Empirical support for this assumption was obtained in our abovementioned longitudinal study, as the persistence of insomnia from baseline to the 2-month evaluation was significantly predicted by higher baseline levels and subsequent increases in maladaptive sleep behaviours, dysfunctional beliefs about sleep, and cognitive monitoring of sleep-related threats [13]. These factors are believed to exert their negative effects by increasing arousal (i.e., physiological, cognitive, and emotional) and performance anxiety, which are in direct opposition to the relaxation state required for sleep.

It is frequent that cancer patients are encouraged to rest and sleep to recuperate from their cancer treatments [72–74], thus leading to maladaptive sleep behaviours, such as napping and spending too much time in bed. In turn, these behaviours reinforce the association of the bed/bedroom with arousal and awakening rather than with sleep. Moreover, In addition to typical faulty beliefs and attitudes about sleep encountered in individuals with chronic insomnia (e.g., "I need 8 h of sleep to function well during the day"), cancer patients entertain certain specific erroneous beliefs including "If I don't sleep well, my cancer will come back", which may induce great levels of arousal and performance anxiety as bedtime approaches ("I really need to sleep tonight"), thus aggravating sleep difficulties. Altogether, these behavioural and cognitive responses may explain the high rate of chronic insomnia observed in patients with a history of cancer and treatment.

13.4 Consequences

Although it is often overlooked in oncology practice, insomnia is not a trivial problem to the patient. Untreated insomnia is very likely to become chronic [12] and to be associated with several negative consequences for daily functioning and quality of life of patients [75–77]. Specific consequences of insomnia in the cancer context have received little attention, but they are likely to be same as, if not worse than those docu-

mented in primary insomnia in general. In particular, the literature has consistently shown that individuals with chronic insomnia are at a higher risk of subsequently developing depressive and anxiety disorders [78, 79], and of having their health negatively affected. Indeed, prospective studies have indicated a greater incidence of physical conditions such as hypertension, pain, and permanent work disability among adults with insomnia [80–83]. In the context of cancer, we found that patients with an insomnia syndrome were at a significantly higher risk of subsequently developing infectious episodes during the cancer care trajectory [84]. Recently, a large epidemiological study investigated the association between sleep duration and quality, and mortality risk. Of the 121,700 female nurses enrolled in 1976, 3682 developed breast cancer. Among them, women who had regular sleep difficulties (as assessed with a single question) had a 49% increased risk of all-cause mortality during the study's follow-up as compared to those who reported little to none. Also, women with a sleep duration ≥9 h post diagnosis were more at risk of breast cancer and all-cause mortality compared to those who slept 8 h [85]. However, such findings need replication.

Importantly, untreated insomnia leads to significant direct and indirect costs for society, that considerably exceed those of an effective insomnia treatment [86]. It is associated with more frequent medical consultations, absenteeism, and reduced work capacity/productivity [75, 83, 86–88]. The importance of systematically screening for sleep disturbances at critical points of the cancer care trajectory is essential for optimal functioning of cancer survivors.

13.5 Evaluation of Sleep Difficulties

Evaluating sleep disturbances in clinical contexts should ideally be a multistep process starting with a rapid screening by first-line providers and, when positive, followed by a more in-depth assessment involving several modalities (see Table 13.2).

13.5.1 Screening Sleep Difficulties

Sleep difficulties are typically under-diagnosed and under-treated in cancer care. On the one hand patients don't spontaneously report their difficulties sleeping to their health care providers [89]. On the other hand, cancer care providers often fail to ask patients about their sleep quality. Hence, actively screening sleep problems on a routine basis is an essential first step in order to ensure that these difficulties are appropriately managed.

Over the past decade, many cancer centers throughout the world have implemented a routine screening procedure of psychological distress, which often contains some assessment of sleep disturbances. For instance, in Canada, the *Edmonton Symptom Assessment Sys*tem (ESAS) [90] and the *Canadian Problem Checklist* (CPC) [91, 92] are used along with the *Distress Thermometer* [93, 94] to screen for psychological distress and other psychological, physical, practical, information, and spiritual issues. These instruments are administered on several occasions at crucial times of patients' cancer care trajectory. The original version of the ESAS included no specific insomnia item but patients could use the "other problem" item to report their sleep difficulties. The ESAS also contains an item assessing drowsiness rated on a "0" to "10" scale, which could be a consequence of insomnia but is more specific to other sleep disorders (e.g., sleep apnea). With regard to the CPC, it contains a sleep item, which is a box that can be checked if the problem is present. The pan-Canadian practice guidelines on sleep disturbances in cancer patients [95] recommended using the "other" item of the ESAS and the CPC-sleep item, but not the CPC-drowsiness item, to identify possible cases, but evidence was lacking at that time to support these recommendations.

A study conducted by our research team investigated the capacity of the ESAS and the CPC to detect patients with a clinical level of insomnia on the *Insomnia Severity Index* (ISI) in 615 patients with various cancer types [96]. It was concluded: (a) that the CPC-other item was ineffective since none of the patients used this item to

Table 13.2 Assessment methods for sleep difficulties

Measure	Comment
Screening	
Edmonton symptom assessment system (ESAS) [96] and Canadian problem checklist (CPC) [91, 92]	Use a combination of criteria: Positive answer on the CPC-sleep item OR a score of 2 or greater on the ESAS-drowsiness item OR add a sleep item to the ESAS
National Institutes of Health patient-reported outcomes measurement information system (PROMIS) [97]	Comprises two sleep items
Clinical interview	
Duke structured interview for sleep disorders [99]	Comprises four modules: Insomnia disorders, sleep disorders associated with excessive daytime sleepiness and hypersomnia, circadian rhythm disorders, and parasomnias
Insomnia interview schedule [14]	Assess the nature (e.g., problems falling asleep, staying asleep) and evolution of sleep disturbances (e.g., time of onset, chronicity, triggering factors)
Sleep diary	
Consensus sleep diary [103]	1–2 weeks Assess the daily variations in various sleep parameters assessed subjectively (e.g., total wake time, sleep efficiency)
Questionnaires	
Insomnia severity index [14, 104]	7-item questionnaire that evaluates insomnia severity specifically A score ≥ 8 indicates the presence of a clinical level of insomnia A score ≥ 15 suggests the presence of an insomnia syndrome
Pittsburgh sleep quality index [106]	19-item self-report scale that provides a measure of general sleep disturbance A score > 5 suggests the presence of clinically significant sleep difficulties
Epworth sleepiness scale [108]	8-item questionnaire assessing daytime sleepiness
Dysfunctional beliefs and attitudes about sleep scale [109]	Evaluates typical erroneous beliefs about sleep among insomnia patients
Sleep behaviour self-rating scale [110]	Assesses sleep-incompatible behaviours that are typically associated with insomnia
Sleep associated monitoring index [111]	Evaluates presleep, waking and daytime monitoring of sleep-related threats
Sleep preoccupation scale [112]	Measures sleep-related daytime preoccupations
Objective measures	
Polysomnography	Includes electroencephalography, electro-oculography and electromyography Ambulatory/laboratory Allows an objective assessment of sleep parameters (e.g., total wake time, sleep onset latency) and the quantification of sleep stages Detects sleep disorders such as obstructive sleep apnea and periodic limb movement disorder
Actigraphy	Objectively quantifies sleep parameters and characterizes rest-activity cycles

report their sleep difficulties; (b) that neither the CPC-sleep and ESAS-drowsiness item provided an optimal screen for clinical insomnia when used alone; and (c) that a valuable alternative was to use a positive answer on the CPC-sleep item OR a score of 2 or greater on the ESAS-drowsiness item. This combination of criteria yielded a sensitivity of 84.2% and a specificity of 69.7%. However, given that using a combination of information is less practical for first-line cancer care providers, an alternative could be to add a sleep item to the ESAS, as other authors have done. Depending on the version used, the ESAS-sleep item is rated from "0" (best sleep) to "10" (worst sleep imaginable) or from "0" (no trouble sleeping) to "10" (worst sleep imaginable). One study conducted in advanced cancer patients found that a score of 3 or higher on such an item

was associated with a sensitivity of 74% and specificity of 73% when compared to a score greater than 5 on the *Pittsburgh Sleep Quality Index* (PSQI) [28]. Studies are needed to assess the screening capacity of this item in the context of early cancer.

Other options exist to screen for sleep difficulties. The above-mentioned Canadian practice guidelines also suggests using two sleep items from the bank of items of the *National Institutes of Health Patient-Reported Outcomes Measurement Information System* (PROMIS) [97]. These questions are: "Do you have problems with your sleep or sleep disturbance on average (routinely, in the past month, etc.) For three or more nights a week?" and "If yes, does the problem with your sleep negatively affect your daytime function or quality of life?" To our knowledge, the diagnostic accuracy of these two specific questions to screen for clinical levels of insomnia has not been investigated. However, a recent study assessed the screening capacity of the sleep disturbance and sleep-related impairment items on the PROMIS computerized adaptive testing (CAT) in 336 patients with mixed cancer sites [98]. The PROMIS CAT automatically selects 4 to 7 items from a larger bank based on patients' first responses. The results of this study indicated that, when compared to an ISI score of 8 or greater, a T-score of 53 on the PROMIS CAT measure of sleep disturbance led to a sensitivity of 82.2% and a specificity of 82.8%, while a T-score of 53 for sleep-related impairment was related to a sensitivity of 77.1% and a specificity of 81.0%. While the tailoring of this type of assessment to each patient is interesting, it does not significantly reduce the time of administration as compared to existing measures (7 items for the ISI), thus questioning its implementability in routine care.

13.5.2 Clinical Interview

A positive screening of sleep disturbance should be followed by a clinical interview that provides health providers the opportunity to assess aspects such as the exact nature of the sleep disturbance; its duration, triggers and the personal sleep history. Ideally, if time allows a semi-structured interview should be used. The *Duke Structured Interview for Sleep Disorders* (DSISD) is an effective tool to assess the presence of several sleep disorders based on the DSM and ICSD classifications and to make a differential diagnosis [99]. It is divided into four modules assessing: insomnia disorders, sleep disorders associated with excessive daytime sleepiness and hypersomnia, circadian rhythm disorders, and parasomnias. It is important to distinguish insomnia from other sleep disorders such as obstructive sleep apnea (OSA) because this will determine the type of treatment to initiate (e.g., cognitive-behavioural therapy for insomnia vs. continuous positive airway pressure for OSA).

A semi-structured clinical interview, such as the *Insomnia Interview Schedule* [14], is also useful to gather details on the nature (e.g., problems falling asleep, staying asleep) and evolution of sleep disturbances (e.g., time of onset, chronicity, triggering factors) as well as information helpful to guide intervention (e.g., usual sleep schedule, maladaptive sleep behaviours, utilization of sleep medication, other health habits that may influence sleep).

Other semi-structured interviews that can be used include the *Structured Interview for Sleep Disorders* [100] and the *Structured Diagnostic Interview for Sleep Patterns and Disorders* [101]. Interestingly, the research version of the *Structured Clinical Interview for DSM-5* (SCID-5) [102] includes a module assessing the presence of the insomnia disorder, the hypersomnolence disorder and the substance/medication-induced sleep disorder based on DSM-5 criteria.

13.5.3 Sleep Diary

A daily sleep diary (SD) such as the Consensus Sleep Diary [103] is a valuable tool to assess the daily variations in various sleep parameters assessed subjectively (e.g., SOL, WASO, SE). It is usually filled out every day for 1 or 2 weeks to establish a baseline before the introduction of an intervention and at post-treatment to assess its

effects. It is also helpful – if not necessary – to have it completed by the patient during the intervention to monitor progress and to guide the application of sleep restriction (see description below). Several formats of SD have been used in research and clinical practice but it typically collects information on bedtime, time to fall asleep, number and duration of nocturnal awakenings, time of last awakening, rising time, and napping. Based on an analysis of the various SD forms used by a committee of sleep experts in their own work and in order to facilitate comparisons across studies, a consensus SD was developed [103].

13.5.4 Questionnaires

A variety of self-report scales are commonly used to assess the nature and severity of sleep disturbances. The ISI [14, 104] is a 7-item questionnaire that evaluates insomnia severity specifically. This scale was validated in cancer patients [105]. A score of 8 or higher indicates the presence of a clinical level of insomnia, whereas a score of 15 or higher suggests the presence of an insomnia syndrome. The PSQI [106] is a 19-item self-report scale that provides a measure of general sleep disturbance. A total PSQI score greater than 5 is the cut-off generally used to distinguish patients with clinically significant sleep difficulties, including insomnia [107]. Besides, administration of the *Epworth Sleepiness Scale* [108], an 8-item questionnaire, is indicated when patients' chief complaints include daytime sleepiness.

Other questionnaires are valuable to guide the implementation of cognitive-behavioural strategies such as the *Dysfunctional Beliefs and Attitudes about Sleep scale* [109], which evaluates typical erroneous beliefs about sleep among insomnia patients ("I need 8 hours of sleep to feel refreshed and function well during the day"), the *Sleep Behavior Self-Rating Scale* [110], which assesses sleep-incompatible behaviours that are typically associated with insomnia (e.g., "I spend a lot of time lying awake in bed at night"), the *Sleep Associated Monitoring Index* [111], which evaluates presleep, waking and daytime monitoring of sleep-related threats (e.g., "calculate the number of hours of sleep you are likely to get") and the *Sleep Preoccupation Scale* [112], which provides estimates of sleep-related daytime preoccupations (e.g., "I worry about the long-term consequences of poor sleep"). None of these questionnaires have been validated in cancer patients.

13.5.5 Objective Measures

A polysomnographic evaluation involves all-night electrophysiological monitoring as measured by electroencephalography, electrooculography and electromyography. Polysomnography (PSG) is considered the gold standard measure of sleep. An overnight PSG evaluation can take place in a laboratory or at home (ambulatory). Unique features of PSG are that, in addition to providing an objective assessment of sleep parameters (e.g., SOL, WASO), it distinguishes between wake and sleep and permits the quantification of sleep stages. Moreover, a PSG study is an essential component of the evaluation when there is a suspicion of sleep disorders such as OSA and periodic limb movement disorder which can only be diagnosed by this method. Otherwise, because of the costs involved and the lack of accessibility, a PSG recording is not indicated for the routine evaluation of insomnia [113]. Additionally, PSG does not take into account the subjective aspect of insomnia. Yet, dissatisfaction with sleep and a perceived negative impact of insomnia on daytime functioning and significant distress are core features of insomnia (DSM-5) [114]. Reactivity to the measure and the lack of ecological validity, especially when performed in a laboratory, are other limitations of PSG.

Actigraphy has increasingly been used in research over the past years to objectively quantify sleep parameters and characterize sleep-wake cycles. Actigraphy recorders are small non-intrusive devices that are worn on the wrist. By calculating orientation and movement, actigraphic devices do not distinguish sleep from wake but estimations of wake and sleep time are made using specific algorithms. Obviously, this measure is not as precise as

Table 13.3 Main symptoms of sleep-wake disorder other than insomnia

Disorder	Main symptoms
Obstructive sleep apnea	Loud snoring, pauses in breathing during sleep, restless and fragmented sleep, excessive daytime sleepiness
Periodic limb movement disorder	Repetitive, highly stereotyped movements of the limbs (legs and arms) occurring during sleep, sleep fragmentation, excessive daytime sleepiness
Restless legs syndrome	Uncomfortable aching sensation in the legs and irresistible urge to move them at rest, at any time during the day (but usually worse at bedtime), prolonged sleep-onset latency
Hypersomnolence	Excessive daytime sleepiness, recurrent periods of sleep or lapses into sleep within the same day, prolonged main sleep period, nonrestorative sleep, difficulty being fully awake after abrupt awakening
Narcolepsy	Recurrent and unpredictable/uncontrollable sleep attacks throughout the day, excessive daytime sleepiness, sleep paralysis, hypnagogic hallucinations, and cataplexy
Circadian rhythm sleep disorders	Misalignment between the individual's sleep-wake rhythm and the desired or the "normal" sleep-wake schedule (delayed sleep phase type: Sleep onset late in the night, difficulties waking up in the morning; advanced sleep phase type: Early sleep onset and morning awakening)

PSG. For instance, wake time in bed can erroneously be scored as sleep time if the sleeper is immobile. Like PSG, actigraphy does not take into account the subjective nature of insomnia. Hence, although actigraphy is less costly than PSG and has a better ecological validity, its use is usually not indicated in clinical contexts.

Several commercial sleep trackers have been marketed in recent years, but their validity is questionable. A systematic review compared consumer-wearable activity and sleep trackers to PSG and showed that commercial devices tended to overestimate total sleep time and SE, and to underestimate WASO, as compared with PSG [115]. This represents a considerable limitation for their use in clinical and research settings.

13.5.6 Indications for Referral

It is essential to refer to a specialized sleep physician patients with a suspicion of a sleep disorder other than insomnia (see Table 13.3 for clinical manifestations of these disorders). When the chief complaint is excessive daytime sleepiness, referral to a sleep disorders center can be helpful. In addition to a nocturnal PSG, a daytime testing will be conducted to evaluate the severity of patients' sleepiness. A referral to a specialized sleep clinic is also indicated when the insomnia treatment initially administered (e.g., cognitive-behavioural therapy) is not successful.

13.6 Interventions

13.6.1 Current Clinical Recommendations

Pharmacotherapy (mostly sedative/hypnotics) is almost always the first treatment prescribed for sleep disturbances. However, this trend is not consistent with the National Institutes of Health (NIH) and American College of Physicians recommendations to introduce cognitive-behavioural therapy (CBT) as the initial treatment for chronic insomnia in adults [116, 117]. CBT for insomnia (CBT-I) is also recommended as the first-line treatment for sleep disturbances among cancer patients [95, 118]. The infrequent use of CBT-I may be explained by the fact that cancer care providers are usually unaware of the existence of effective non-pharmacological options for insomnia, and that these alternatives are rarely easily accessible in their clinical settings. Indeed, there are very few psychosocial oncology professionals formally trained to administer CBT-I, and those who are struggle to meet all their patients' needs given the high prevalence of insomnia symptoms in this population. We describe CBT-I in more detail below.

13.6.2 Hypnotic Medications

Most commonly prescribed hypnotic prescriptions in cancer are benzodiazepines with sedative and/or hypnotic properties (e.g., lorazepam, oxazepam) and the newer non-benzodiazepine hypnotics (e.g., eszopiclone, zolpidem).

Rates of utilization Recent epidemiological data from France indicate that a prescription of psychotropic drugs is made in about one in two patients (52%) in the first year following the cancer diagnosis [119], which is significantly higher than in individuals with no cancer. In that study, anxiolytics and hypnotics were the most frequently prescribed medications. The rate of hypnotic use was 25% in the first year, which slightly decreased to 17% in the second year post-diagnosis (as compared with a 10% rate in matched individuals with no cancer). Another study conducted among 1984 Canadian cancer survivors found similar consumption rates. About 41% reported having received a prescription for a hypnotic since their cancer diagnosis, and 23% were currently using one, with a mean duration of 58.1 months [3].

Efficacy No study has yet been conducted to assess the efficacy and tolerability of sleep medications in cancer. Thus, the risk-benefit ratio of these drugs is unknown in oncology, in particular with regard to their long-term usage. In the general population, a meta-analysis of 13 studies comprising 4378 participants revealed that non-benzodiazepines (e.g., eszopiclone) had a significantly greater effect on objectively recorded SOL (−22 min) as compared with placebo, while the other outcomes (total sleep time, +14.1 min, WASO, −7.1 min) showed no significant differences [120]. Moreover, according to the clinical guidelines of the American College of Physicians, there is still insufficient evidence about the balance of benefits and harms of long-term use of benzodiazepine hypnotics in the management of chronic insomnia [117, 121].

Besides, there is some preliminary evidence supporting the efficacy of exogenous melatonin among cancer patients with insomnia [122]. In a small-scale randomized-controlled trial (RCT), 50 cancer patients (mixed sites, stage I-IV) with an insomnia syndrome were randomized to either melatonin 3 mg at 7 pm, or a placebo, for 14 days. Improvements of perceived sleep quality that were clinically and statistically larger, as measured with the Athens Insomnia Scale, were observed among the melatonin group relative to the placebo group. These promising results need to be replicated in larger studies. This is important because cancer patients often look for alternatives to prescribed medications and treatments that are more natural and with a safer profile.

Risks and limitations Observational studies highlighted the increased risk for serious adverse effects such as dementia, fractures, and major injury with long-term hypnotic use (e.g., benzodiazepines) [123–125]. Other recognized side effects of hypnotic medications include daytime sedation, anterograde amnesia, and cognitive impairments [126]. Because of their slower metabolism, elderly people are more vulnerable to experience these effects. This is of concern as the median age of cancer patients at diagnosis is 66 years old [127]. Importantly, a chronic usage of benzodiazepines (as well as non-benzodiazepine drugs to a lesser extent) is associated with tolerance and dependence as well as reduced deep sleep (i.e., stage 3 and 4) [128, 129].

Appropriate use of hypnotic medications These limitations have led sleep experts to recommend using hypnotic medications primarily for situational and transient insomnia and to use the lowest effective dosage of hypnotics for the shortest period of time. More specifically, the NIH recommends limiting the daily usage of hypnotic medications to 4–6 weeks [116]. Occasional usage is also appropriate when sleep is anticipated to be difficult due to some acute stressors (e.g., follow-up appointment with the oncologist).

13.6.3 Cognitive-Behavioural Therapy

Description CBT-I targets the behavioural and cognitive factors that are believed to maintain insomnia over time. Thus, it directly addresses the perpetuating factors explained above, in

accordance with the Spielman's model [46]. CBT-I is a multifaceted treatment whose main core components are psychoeducation, stimulus control, sleep restriction, cognitive restructuring, and sleep hygiene (see Table 13.4), and there is evidence that this full package must be delivered in order to reach its maximal efficacy [130]. Relaxation, which is also sometimes offered as part of CBT-I, has been found to be the least effective strategy when used alone and compared to full CBT-I and behavioural therapy [131]. It may also exacerbate performance anxiety in some patients ("I must relax in order to sleep well"), which is counterproductive. CBT-I typically involves 4–6 one-hour sessions, with some data suggesting that four biweekly sessions (i.e., over 8 weeks) would represent the optimal dosage for this intervention [132].

Stimulus control therapy aims at re-associating the bed and the bedroom with sleep and at establishing a regular sleep–wake cycle [133]. It encompasses a series of behaviour changes that the patient is encouraged to adopt (see Table 13.4).

Sleep restriction aims at limiting the time in bed to the actual total sleep time, which creates a mild sleep deprivation facilitating sleep onset and resulting in more consolidated and more efficient sleep [134]. The prescribed duration of the maximal time spent in bed is determined using data (average total sleep time) from the SD completed during the baseline phase. Then, time in bed is progressively increased (by typically 15–30 min) as SE (total sleep time/total time spent in bed) improves and exceeds 85%.

Cognitive restructuring targets dysfunctional thoughts and beliefs about sleep difficulties and their consequences, with the aim of decreasing arousal and performance anxiety towards sleep. The clinician guides the patient to identify maladaptive sleep cognitions (e.g., "If I don't sleep well, my cancer will come back"), challenging their validity, and reframing them into more adaptive substitutes [14, 135]. Patients are also encouraged to generalize the use of cognitive restructuring to other thoughts and worries provoking arousal and that might interfere with sleep.

Table 13.4 Summary of CBT components

Intervention	Description
Psychoeducation	Basic information provided on sleep (e.g., stages, the effect of aging on sleep) and on insomnia (e.g., the 3Ps model of insomnia, the vicious circle of insomnia)
Stimulus control	Allocate at least an hour to unwind before going to bed Go to bed only when sleepy When unable to fall asleep or go back to sleep within 20 to 30 min, leave the bedroom and return to bed only when sleepy again Use the bed/bedroom for sleep and sexual activities only (e.g., do not use electronic devices, watch television, listen to the radio, eat, or read in the bed) Get out of bed at the same time every morning Avoid napping during the day
Sleep restriction	Restrict the amount of time spent in bed to the actual total sleep time (based on past week sleep diary) Time in bed is progressively increased (by 20 to 30 min) as sleep efficiency improves and exceeds 85%
Cognitive restructuring	Identification of dysfunctional thoughts and beliefs about sleep difficulties and their consequences Challenge their validity (by using Socratic questioning such as: "what is the evidence that supports this idea? Is there an alternative explanation?") Reframe dysfunctional cognitions into more adaptive substitutes Generalize the use of cognitive restructuring to other thoughts and worries provoking arousal at night and that might interfere with sleep
Sleep hygiene	Review of the effects of environmental (e.g., bedroom temperature) and lifestyle factors (e.g., caffeine, exercise) on sleep

Sleep hygiene information is also offered, although this component only plays a modest role in treatment effects. The effects of environmental (e.g., bedroom temperature) and lifestyle factors (e.g., caffeine, exercise) on sleep are reviewed and strategies are offered to counteract their influence.

Finally, it is important to conclude the treatment with relapse prevention strategies in order

to ensure the sustainment of therapeutic gains in the long term. More precisely, high-risk situations that are likely to precipitate an insomnia relapse in the future are identified and a plan of action is designed.

Efficacy The efficacy of CBT-I is well established both for primary and comorbid insomnia [136, 137]. In cancer patients, a meta-analysis of the available evidence up until 2014, including eight studies and 752 participants, reported significant improvements associated with CBT-I, with medium to large effect sizes relative to controls for SE (+15.5%; effect size: $d = 0.53$), SOL (−22 min; $d = 0.43$), WASO (−30 min; $d = 0.41$), and self-reported insomnia severity (a 8-point reduction; $d = 0.77$) [138]. Of note, these post-treatment beneficial effects were well sustained 6 months later.

Accessibility in Cancer Care and Acceptability/Efficacy of Alternative Formats of CBT-I Despite the important needs, access to professionally administered CBT-I in cancer care is highly limited. Indeed, there are very few psychosocial oncology professionals formally trained to administer CBT-I. Self-administered treatments, particularly web-based interventions, have gained in popularity in recent years as a way to increase patients' access to this treatment. These approaches represent interesting alternatives to standard face-to-face psychological interventions, and several clinical trials support their efficacy in primary insomnia [139, 140]. Concerning specifically the web-based interventions, several programs have been developed (e.g., SHUTi, sleepio) and empirically tested among the general population [141, 142] and may represent useful tools for cancer patients as well. But, evidence for their efficacy in insomnia comorbid with cancer is scarce. One small-scale RCT conducted in 28 cancer survivors with insomnia revealed that patients assigned to a web-based CBT-I had significantly greater sleep improvements at post-treatment than control participants [143]. However, large-scale studies are needed to verify whether treatment effects of such self-administered programs are of a similar magnitude than those obtained in more standard face-to-face CBT-I.

Following a small-scale study which provided encouraging results [144], we conducted an RCT among 242 breast cancer patients comparing the efficacy of a video-based CBT-I to a professionally-administered CBT-I and a control (no treatment) condition [145, 146] The self-administered intervention was found to produce superior effects as compared to the control condition on several sleep parameters (including ISI and SE assessed with a SD), but the professionally administered CBT-I led to significantly larger effects than the video-based intervention on insomnia severity (ISI) and other outcomes (e.g., depression). Moreover, the remission rate of insomnia at post-treatment was significantly greater among participants who received the professionally administered intervention (ISI score lower than 8: 71.3% vs. 44.3% for the self-administered intervention). However, treatment gains were well sustained up to 12 months post-intervention in both treatment groups [146]. Overall, results of this study are consistent with findings of a meta-analysis indicating smaller treatment effects for self-help interventions for insomnia in general, as compared to face-to-face therapy [139]. However, self-administered CBT-I can be sufficient for many patients and constitutes an acceptable alternative when professionally administered CBT-I is not available, which is the case in many clinical settings, or as a first step of a stepped care model.

Moderators of Treatment Effects Despite the large number of RCTs conducted on the efficacy of CBT-I, very few studies have specifically investigated predictors of treatment outcomes. Thus, it is still unclear for whom and under what circumstances CBT-I is the most beneficial. This is important in order to be able to better orient the provision of care (e.g., offering a face-to-face intervention from the outset to patients who are less likely to benefit from a self-administered treatment) and thus, to maximize the cost-effectiveness of the intervention.

In a secondary analysis of the above-described RCT comparing face-to-face vs. self-administered CBT-I, we investigated the moderators of the video-based intervention received by 81 breast cancer patients with insomnia [147]. Results showed that patients with a more advanced disease (and thus presumably with more disruptive cancer

symptoms) were less likely to show improvements on insomnia severity (ISI) and subjectively assessed SE following the intervention. Remission of insomnia following the self-help treatment was more likely among those with a higher income, and those using antidepressants, which may be explained by a better management of depressive symptoms and hot flashes with medication. However, when using a multivariate binary classification tree analysis, the best and unique predictor of insomnia remission was having a less severe baseline ISI score. These data suggest that patients with more severe insomnia would derive greater benefits from a more intensive intervention from the start, such as a face-to-face treatment.

More research is needed on moderators of CBT-I effects in particular in the context of self-administered formats. Other possible moderators that might need to be taken into account in treatment selection and that should be examined include health literacy (i.e., the basic set of skills to seek, understand, and use health information) and self-efficacy.

Stepped Care Model: The Ideal Approach to Make CBT-I More Accessible to Cancer Patients A stepped care approach represents a cost-effective strategy to increase patients' access to CBT-I [148]. In such an approach, a self-administered intervention generally constitutes the entry level, except for those not expected to sufficiently benefit from this format (e.g., more severe insomnia). Then, patients who go into remission following such minimal treatment receive no further intervention, while others "step up" to a more intense form, such as professionally administered sessions [149]. Consequently, resource allocation in therapy is maximized and treatment costs are significantly reduced [150].

This approach appears especially valuable in the cancer context where the needs for insomnia treatment are high, while the resources are limited. However, its utility and cost-effectiveness have yet to be documented before it is integrated in routine care. To that end, we are currently conducting an RCT comparing the efficacy and cost-effectiveness of a stepped care approach, integrating a web-based intervention (www.insomnet.com), with a standard face-to-face CBT-I in patients with various cancer types.

13.6.4 Other Non-pharmacological Interventions

Other non-pharmacological treatments have been tested for improving the sleep of cancer patients. Of these, physical exercise and mindfulness-based interventions have received the most attention.

Mindfulness-based Stress Reduction Early, uncontrolled studies conducted on the effect of mindfulness-based stress reduction (MBSR) on sleep showed promising results in cancer patients [151, 152]. However, more recent RCTs revealed more mitigated results, showing either no effect on subjective sleep estimates [153], or no long-term sustainment of therapeutic gains 12 months later [154], when compared with a control condition. Using a non-inferiority research design, Garland et al. [155] compared an 8-session CBT-I to a mindfulness-based cancer recovery intervention (MBCR, an adaptation of MBSR) among 111 patients with various types of cancer. MBCR led to a significantly inferior reduction of insomnia severity at post treatment, but became non-inferior to CBT-I at the 3-month follow-up. This suggests that CBT-I is associated with faster improvements and we concur with the authors' conclusion that CBT-I should still be considered the treatment of choice for improving cancer-related insomnia.

Exercise Given the well-recognized positive effects of physical exercise on quality of life of cancer patients [156, 157], significant beneficial effects on sleep might be expected as well. A recent systematic review and meta-analysis of 21 clinical trials, including 17 RCTs, examined the effect of exercise interventions on the sleep of cancer patients [158]. Although about half of the studies (48%) concluded to a favourable effect of exercise, the meta-analysis showed no significant effect on sleep variables, either assessed subjectively or objectively. However, most of these studies assessed sleep as a second-

ary outcome, and the presence of clinical insomnia was typically not a prerequisite to participate. On the one hand, the lack of significant treatment effects may therefore be due to floor effects (e.g., more difficult to improve sleep of good sleepers). On the other hand, it is unclear whether physical exercise interventions are potent enough to efficaciously treat cancer individuals with clinical insomnia. Comparative studies with CBT-I are especially needed to determine whether physical exercise interventions represent a valuable alternative to treat these patients.

13.6.5 Prevention

The ultimate way to decrease the burden of insomnia in cancer care would be to use preventive approaches. In addition to making it possible to avoid the consequences of insomnia on the patient and society, prevention would have the advantage of being less costly. However, research assessing the feasibility and effectiveness of sleep promotion or prevention of insomnia in clinical milieus are still in their infancy.

Berger and her colleagues developed the Individualized Sleep Promotion Plan (ISPP), an adaptation of CBT-I, and assessed its effects in women undergoing chemotherapy for breast cancer [159, 160]. The intent of the intervention was mostly to prevent insomnia symptoms from developing/aggravating during chemotherapy, although a certain proportion of patients already had sleep difficulties at baseline. Sleep quality (as evaluated with the *Pittsburgh Sleep Quality Index*) and the number of awakenings, WASO, and SE significantly improved immediately after the ISPP intervention [161]. However, no long-term between-groups differences were found on any sleep diary (and actigraphic) parameter 1 year later [162]. Our research team has recently developed a preventive intervention, using CBT-I strategies outlined in a short booklet, specifically targeting breast cancer patients about to begin chemotherapy. A pilot study of 20 women has just been completed and the analysis of findings is underway. A major challenge of these studies is to interest patients in receiving an intervention for a problem that they don't yet have and to develop a preventive program that is well accepted by the patients while being powerful enough to prevent the incidence of insomnia during the cancer journey.

13.7 Future Directions

The significance of sleep difficulties among cancer patients is now well recognized and research has provided a better understanding of some cancer-related factors contributing to this problem. Medications have a limited efficacy when used on a daily and chronic basis, and their daily usage should be restricted to the management of acute insomnia and for a duration of 4–6 weeks maximum. CBT-I is recommended as the first-line treatment for insomnia in oncology. Its accessibility, unfortunately too limited, could be increased by using self-administered interventions (e.g., web-based) and stepped care programs, but the effectiveness of these approaches needs to be ascertained before they are integrated into routine care. The efficacy of other non-pharmacological interventions (e.g., mindfulness, exercise) also has yet to be confirmed to treat cancer-related insomnia, as well the feasibility and usefulness of preventive approaches. Referral for a sleep specialist is advised when there is a suspicion of a sleep disorder other than insomnia (e.g., obstructive sleep apnea) or when CBT-I is found ineffective.

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Interpersonal Relationships

14

Tim Regan, Chiara Acquati, and Tania Zimmerman

14.1 The Impact of Cancer on Patients and Partners

Despite the growing number of cancer survivors, a cancer diagnosis remains a life-threatening disease that can result in psychosocial, emotional, and physical distress even years after the medical treatment has ended [1]. A cancer diagnosis not only affects the patient but also significant others. There is a strong association between social support and quality of life among cancer survivors. Perceiving more social support from significant others is related to more successful coping with the challenges of the cancer diagnosis and beyond, including dealing with anxiety and depression, employment and financial problems as well as healthy lifestyle and positive attitudes [2]. For most cancer survivors, the spouse/partner emerged as the most significant source of social support [3]. Nevertheless, cancer can affect both members of the dyad and spouses/partners also experience psychosocial distress.

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Psychological distress is common among cancer survivors and has been reported in 20–30% of cancer patients [4, 5]. The extent of psychological distress among survivors can range from normal adjustment levels to those that meet diagnostic criteria for mental health disorder. Approximately 40% of cancer patients show significant distress [6]. While type of disease is only modestly related to distress, patients with pancreatic, brain, and lung cancer seem more likely to express distress [7]. Being female, poorer functional performance as well as more psychosocial (e.g. dealing with children, partner) and emotional (e.g. depression, fears, sadness, worry) problems emerged as related to distress [8]. Although most patients adjust well to cancer, understanding distressing experiences among this population is crucial because, when experienced, the negative psychosocial impacts can be significant. Some common areas of distress experienced by many cancer survivors for example include: fear of cancer recurrence, increased sense of vulnerability, lowered sense of control, concerns about body image and sexuality [9].

Approximately 44% of cancer survivors experience anxiety, and 23% experience anxiety that meet criteria for a clinical disorder [10]. Anxiety reactions can be either time limited or more prolonged or intense. The prevalence of depression is approximately 12.5% [11] and associated with more frequent and longer hospitalizations, lower quality of life and decreased compliance to treatment [12]. In women with

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breast cancer, older breast cancer survivors experience overall better quality of life and mental health than younger women, but they tend to have poorer physical health and health-related quality of life due to comorbid conditions [13]. Adjustment to the disease is of great importance; hence survivors with poorer adjustment tend to have greater medical problems, poorer premorbid psychological adjustment, fewer economic resources and fewer social supports [14].

Partners report similar emotional reactions to a cancer diagnosis as patients (e.g., fear, shock, anxiety) [15], and some studies have suggested that partners may experience these feelings to a greater degree than patients [16, 17]. The prevalence of depression and anxiety in spouses of cancer patients vary between 10–53% and 16–56%, respectively [18]. In addition to the shock of diagnosis, the partner may have to adjust to role change; interruption to daily life, financial worries and strain on marital and sexual satisfaction. Caregivers experience numerous types of burden including physical, psychosocial and financial difficulties [19–21]. Higher risks for stress and burnout have been reported, with spouses' emotional distress higher or as high as the levels reported by the patients [22, 23]. Moreover, caregivers can experience high levels of anxiety and depression, impaired sleep and other health-related issues [1, 2]. The responsibilities associated with caregiving also can affect health-promoting behaviors, with less than optimal levels of physical activity attributable to the role and its demands [3, 4].

Cancer-related problems can lead to chronic stress that can impact close relationships and may lead to dissolution. Research on marital strain and cancer is conflicting with some studies observing an association between cancer and relationship dissolution while others claim that dissolutions post-diagnosis are uncommon and cancer survivors are not at greater risk for divorce than the general population [5]. Some studies found gender differences in the extent to which specific cancer-related problems were related to separation. Stephens et al. [5] demonstrated a higher risk of divorce or separation for women after cancer diagnosis. In addition, for both male and female cancer survivors, lower income, younger age (<65 years), and longer time since diagnosis were associated with greater odds of separation.

14.2 Dyadic Stress and Dyadic Coping

14.2.1 Cancer from a Relational Perspective

A relational perspective in the context of cancer is supported by the fact that one of the unique aspects of this experience is the interdependence of partners' responses and coping strategies. As patients' adjustment is greatly influenced by interpersonal closeness and the quality of their significant relationships, partners play an essential role in providing physical, emotional, spiritual or practical support [6–9]. Similarly, patients' reaction to cancer can influence the partners' physical and psychological well-being [1, 10]. The bond between patients and their significant ones is particularly evident as caregivers are called to adjust to the impact of the diagnosis on the individual's well-being, participate in the decision-making about cancer treatment, and cope with changes in occupation and family organization [11–16]. Although the emotional and social needs of informal cancer caregivers have been overlooked in the past [17], supportive partners are crucial for the psychosocial well-being of patients and dyads over time [10, 18–21]. Based Berg and Upchurch's [22] view of dyadic coping, Figure one outlines the broad processes that occur when considering the impact of cancer on patients and their partners from a relational perspective (Fig. 14.1).

14.2.2 Quality of Life and Emotional Well-being

The quality of life of both partners is negatively impacted by the illness, with patients and partners' scoring below that of the healthy population [7, 14, 23–28]. Impairments in emotional, physi-

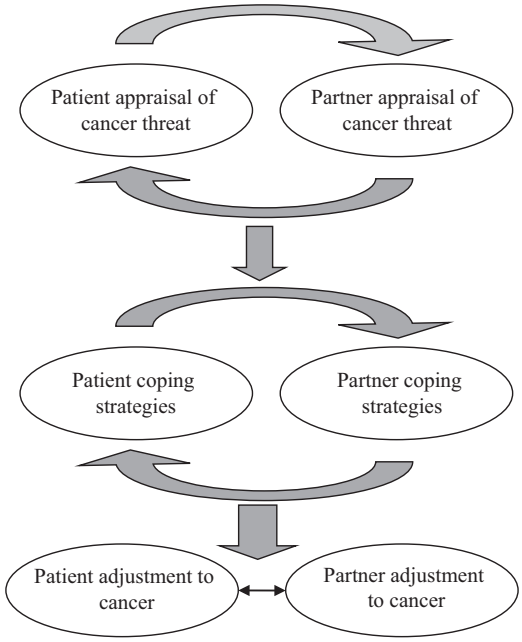

Fig. 14.1 Relational processes involved in appraisal, coping, and adjustment to cancer for patients and their partners. (Adapted from Berg and Upchurch [22])

cal and social function have been documented in patients for years; partners are also at higher risk for worse health-related quality of life, anxiety and illness intrusiveness over time [1, 23, 29, 30].

A pattern of interaction, although moderate, has been identified between each partners' level of distress [1, 31–34], suggesting that the stress associated with cancer is interpersonal in nature. Longitudinal studies have confirmed these results, with association between partners' distress and similar trajectories of functioning within the couple emerge [35–40]. Distress scores of patients and partners are not only associated, but some studies have identified that distress is the strongest predictor of quality of life in both members of the dyad [32]. Hence, the couple reacts to cancer as an "emotional system", with a reciprocal influence on each other's well-being and interdependent emotional responses [7, 21, 41].

Psychological distress is an important aspect of risk for the couple coping with cancer, because of its association with negative communication, reduced intimacy and lower levels of emotional well-being [42]. Partners' interdependence of quality of life has been supported also when depression, anxiety, physical have been investigated. Graca Pereira, Figuereido, and Fincham [43] found that higher scores on depressive symptoms were observed among partners of depressed cancer patients. Drabe,Wittman, Zwahlen, Buchi, and Jenewein [44] observed that approximately 40% of variance in female patients' depression was explained by partners' stress and coping resources. Low levels of functioning in general life domains had a spillover effect on the marital and sexual quality of the relationship [39]. These effects are maintained over long-term. For example, Litzelman & Yabroff [45] reported that cancer survivors whose spouses reported depressed mood at diagnosis were more likely to report depression again 8 years later. In the same study better mental and physical health-related quality of life of partners at baseline were associated with a 30% reduction in survivors' depressed mood risk, indicating that depression and poor health quality of life in partners may increase risk of depression for cancer patients, especially for women [45].

In terms of predictors or correlates of distress, the role of cancer-related variables, demographic and psychological factors has been well established. More recently attention has shifted toward relational factors [46]. Poor conflict resolution skills, pre-illness marital dissatisfaction, lower quality of family functioning, higher conflict rate, low social support, and different perceptions and expectations about the disease are associated with worse psychological well-being for both partners, and higher physical symptoms in the patient [30, 47, 48]. Relationship quality was also predictive of better quality of life in partners of women with breast cancer, while higher mental functioning of the patient was significantly associated with greater physical and mental well-being in the spouse [23]. Improvements in distress outcomes may require more specific attention to relationship issues between cancer survivors and their partners.

14.2.3 Communication

Cancer significantly changes the communication patterns of the dyad, with potentially detrimental effects such as marital dissolution, reduced satisfaction and lack of social support [49–51]. Mutual constructive communication, self-disclosure and more frequent "relationship-talk" have been consistently associated with higher levels of social support, quality of life, better psychological adjustment and relationship functioning for both cancer patients and partners [42, 49–55]. Sharing feelings and concerns has a protective effect on the psychological well-being of cancer patients even when they are experiencing multiple physical symptoms [42, 56, 57].

Differences in communication outcomes also need to be considered in patients and partners. Over time greater levels of communication about the couple relationship were associated with less distress for the partner [49]. However, it must be emphasized that disclosure of thoughts and feelings can be harmful under certain circumstances. For example, contrasting communication styles between two partners, like demand-withdraw communication (i.e., one person demands discussion/change, the other withdraws from discussion) or mutual avoidance (i.e., where partners avoid particular topics), have been associated with higher levels of distress, depression, anxiety, and lower relationship satisfaction [58, 61]. Moreover, there is research that suggests that not only does emotional disclosure not reduce depressive symptoms; it can lead to increases in depression symptoms, when partners were not adequately prepared to discuss one another's emotions regarding cancer [61, 62].

14.2.4 Sexuality and Intimacy

A growing body of evidence has established that cancer dramatically impacts sexual functioning of patients and partners. Data show that approximately half of all patients will encounter a sexual problem during their experience with cancer [63]. Changes in sexual frequency and sexual satisfaction in women with breast cancer have been associated with physical consequences of cancer treatment, psychological factors, body image concerns and relationship characteristics [64–67]. For women, common physical sexual issues include decreased libido, decreased lubrication, and pain [68]. Additionally, breast cancer survivors have reported dissatisfaction with body image post-reconstruction as well as being surprised by changes in breast and nipple sensitivity [69]. For men with prostate cancer, common physical issues can include decreased libido, erectile dysfunction, as well as hot flushes, fatigue and breast swelling [70–72]. Sex specific difficulties are often associated with isolation, anxiety, depression and sense of inadequacy [73–76]. Furthermore, for women with colon or rectal cancers who already present personality traits characterized by high levels of anxiety, this personality characteristic represents an independent predictor of worse quality of sexual life, sexual functioning and sexual enjoyment while coping with cancer [77].

The impact of the disease on the partner is also considerable [78, 79]: fear of initiating sex and difficulties re-building a sense of normalcy in the sexual relationship with the patient have been reported [80, 81]. The dynamics of the caregiving relationship often interfere with the couple's intimate relationship: as the male partner is often providing physical care for the female patient, it becomes challenging to consider the woman as a sexual partner [75, 82, 83]. The presence of sexual dysfunctions has been associated with poorer psychological adjustment in gynaecological cancers [84], and worse quality of life and increased risks of depression in partners in the context of breast cancer [27]. In a more recent study, Moreira and Canavarro [66] confirmed the presence of impaired psychological adjustment of partners of women with breast cancer. However, the authors also highlighted that greater levels of intimacy were associated with reduced depression and greater quality of life for both members of the couple.

Previous research has observed that despite a desire to understand and improve sexual functioning in the context of cancer, both male and females, and patients and partners, are somewhat reluctant to discuss these issues with their medical team [85, 86], and are thus unlikely to initiate conversations about their concerns [87]. Moreover, clinician barriers include limited training and confidence discussing sexuality and a fear of offending or upsetting patients and spouses if they initiate these discussions [88, 89]. To address these barriers, Bober and colleagues [90] suggest clinicians adopt a staged approach based around consensus guidelines checklist [91] and application of the 5As model [92]: Ask, Advise, Assess, Assist, Arrange follow-up. Increasing the skills of clinicians to initiate and facilitate conversations regarding sexuality and validate patient and partner concerns is essential for improving sexuality outcomes in cancer survivors.

14.3 Dyadic Coping and its Role for Individual and Relational Outcomes

A significant association between coping styles, partners' well-being and marital satisfaction has been extensively confirmed in the literature across populations and disciplines [40, 62, 93]. The process of adaptation to the illness is complex and affects both members of the couple [40, 52, 62, 94–97]. From several contributions, it clearly emerges that the ability of the couple to share this experience leads to enhanced couple functioning [96, 98]. While traditional models of stress and coping have concentrated on the individual, in the last 20 years a new attention towards interpersonal aspects of coping has emerged [40, 62, 93, 98–101]. As a consequence, different theoretical frameworks have emerged with the goal of understanding how coping develops within the context of significant relationships [93, 102]. Couples' coping research and practice no longer just focuses on the individual or separate perspectives of the two partners, but considers the dyadic processes involving the partners' mutual influence [103].

The literature supports the idea that dyadic coping should be conceptualized as a process shaped by the context of close relationships [104–106]. It is described as "the interplay between the stress signals of one partner and the coping reactions of the other, a genuine act of shared coping" [105, p. 4]. Dyadic coping contributes to a sense of we-ness and promotes the conjoint creation of strategies to respond to the stressful event [98, 103, 107]. It is described as circular and bi-directional process, with both partners equally involved providing and receiving support from each other while engaging in joint problem-solving activities and shared emotion regulation [100, 103].

The relationship between dyadic coping and marital functioning, better psychological and physical well-being, and lower stress has been established across different populations and couples coping with a variety of stressors (chronic illnesses, depression, anxiety, anger and verbal aggression) [25, 100, 103, 108–113]. When considering the stress of a cancer diagnosis, the ability of the couple to face the illness as a "we-disease" contributes to higher relationship quality and cohesion [39, 108, 114, 115]. Similarly, relationship maintenance behaviors, social support exchanges, mutual constructive communication and joint dyadic coping have been associated with better relationship functioning and quality of life [52, 56, 59–61, 116–118].

Several models of dyadic coping have been developed [40, 62, 99, 119–123]. Although they all share the same view of dyadic coping as a process through which partners cope with the stress they encounter in their life as a couple, each offers unique insight on what dyadic coping is and how it is associated with relational and individual outcomes [9, 39, 62, 93, 122]. A lack of consensus in the conceptualization and assessment of dyadic coping confirms the complexity of the study of human relations during a time of crisis, such as a health condition. An ongoing critical reflection on dyadic coping is crucial to completely understand the relationship between stress and health [40, 100, 102].

14.4 General Theoretical Frameworks of Dyadic Coping Relevant to Cancer Survivorship

14.4.1 Relational-Focused Coping

"Relational-focused coping" emphasizes the cognitive and behavioral efforts to maintain and protect social relationships while coping with stressful events [100, 124] and emphasizes two categories of relationship-focused coping: active engagement and protective buffering [125]. Active engagement refers to the active involvement of one partner in discussion, constructive problem-solving and attention to feelings [126]. Protective buffering describes the behavior of a partner that hides concerns, denies worries and tries to avoid disagreement with the other [125]. Greater active engagement is associated with reduced psychological distress, greater self-efficacy, and greater relationship functioning [127, 128]. In contrast, protective buffering has been linked to negative relational and psychosocial outcomes [53, 125, 127, 128].

14.4.2 Congruence Model

Congruence can involve similar or complementary coping styles: both partners can use emotional or problem-solving coping, while partners may use a more emotional coping style in response to the problem-solving approach of the other spouse [100, 106]. This is not to say dissimilar coping styles are not congruent. In fact, dissimilar styles can be effective as they can provide a broader "coping repertoire" to the couple [100]. For example, a patient with prostate cancer might withdraw from discussion about the cancer or their needs (e.g., emotion-focused coping), their partner might gather relevant information about prostate cancer treatments and also provides them to the patient to read in their own time. Non-congruent strategies, on the contrary, occur when the partners' strategies are aimed at "cancelling each other out" [93, p.8] and are associated with worse psychosocial outcomes [62, 118, 129–131]. For example, where a patient with prostate cancer withdraws from discussion and their partner pushes the partner to discuss their feelings.

14.4.3 Systemic-Transactional Model

Bodenmann's" Systemic-Transactional Model" distinguishes individual coping efforts, where stress is managed independently, from dyadic coping processes in which both partners are involved [103, 104, 132]. An individual's appraisal is communicated to the partner, whom then interprets and decodes the partner's stress signals and responds with a form of dyadic coping [103]. Negative and positive forms of dyadic coping have been distinguished, resulting from different situations occurring in their lives, individual and dyadic appraisal, and partners' competences [93, 103].

Supportive (e.g., listening empathetically to ones' fears) and delegated (e.g., take over certain household chores to reduce burden on other) dyadic coping exemplify positive and adaptive dyadic coping styles, while negative dyadic coping is classified in hostile (e.g., using sarcasm in response to partner's fears), ambivalent (e.g., unwillingly listening to patient's fears) and superficial (e.g., discussing concerns with minimal emotional input) [93, 103, 104]. Positive dyadic coping has been associated with greater positive adjustment to metastatic breast cancer [108] and prostate cancer [133] for patients and their partners. Negative dyadic coping was associated with higher levels of distress and reduced levels of adjustment to metastatic breast cancer by patients and their partners [108], and decreased relationship satisfaction among patients with prostate caner and their partners [133].

14.4.4 Relational-Cultural Model

The "Relational-Cultural Model" of dyadic coping [98] describes how appraisals and responses are shaped by existing relational characteristics. Within this framework, two different patterns of

relational coping have been defined: mutual responsiveness and disengaged avoidance [98, 134]. Couples characterized by mutual responsiveness appraise the stress of cancer as affecting both members of the couple and they initiate a stress communication process that leads to mutually coordinated coping behaviors [98, 134]. In contrast, a disengaged avoidant pattern of coping is characterized by the persistent appraisal of cancer as an individual stressor, and partners' communication lacks expression of emotions and feelings. Hence, at least one partner copes by avoiding or denying the effect of cancer or the coping strategies are limited to problem-solving, with a cascade effect on other significant relationships. The outcome is that partners cannot find any benefit from the experience [98, 122, 134].

14.4.5 Relationship-Intimacy Model

"The Relationship Intimacy Model of Couple Psychosocial Adaptation to Cancer" [135] identifies intimacy as the prime mechanism that enhances or compromises couples' adjustment to stressors [135]. Relationship-enhancing behaviors include mutual self-disclosure (e.g., how couples discuss feelings associated with cancer), partner responsiveness (e.g. the partner understands the individual's thoughts and feelings), and relationship engagement (e.g. acknowledging impact of cancer both on individual and the relationship; engaging in behaviors that enhance the relationship). Relationship-compromising behaviors include avoidance, criticism and demand-withdraw communication (e.g., forcing a partner to discuss cancer-related problems; other member of the dyad withdraws). Greater levels of relationship intimacy and low psychological distress were observed when using mutual constructive communication in couples coping with prostate cancer [136]. Spousal disclosure and perceived support have been associated with greater intimacy and well-being among patients with breast, head and neck, or lung cancer and their partners [58, 137]. In contrast, increased psychological distress has been associated with patient-demand and partner-withdraw communication patterns [58, 137].

14.4.6 Developmental-Contextual Model

Berg and Upchurch [22] suggested that dyadic coping changes across the life-span and is influenced by historical and current events. Changes in appraisal and coping efforts take place over the trajectory of chronic illness [22, 100], with older couples tending to show greater mutuality and less maladaptive coping than younger couples [138–141]. Berg and Upchurch [22] described three dyadic coping processes: collaborative coping, uninvolved coping, and control coping. Collaborative coping refers to partners' equal involvement in shared decision-making [142] and has been found to be associated with positive mood for patients coping with prostate cancer and their partners [143]. Uninvolvement is characterized by the enactment of individual coping strategies in which partners act on their own. Control coping describes behaviors characterized by over-involvement or behavioral control [142, 143], such as a partner taking the lead in clinical consultations, while the patient feels they have little to no input (Table 14.1).

14.5 Implications for Clinical Practice

The last 10 years has seen a significant increase in research output in the context of the adjustment, survivorship and intervention of patients and their partners to cancer. Several couple-based interventions with cancer survivors and their partners have been introduced with the goal to promote relationship functioning and reduce distress. Scott and Kayser [9] and Baik and Adams [144] conducted systematic reviews of psychosocial interventions on cancer survivors and partners evaluated through RCT and quasi-experimental studies, indicated improvements in sexual adjustment [9]. Similar findings have been reported in middle-aged and older adult couples [144]. Other works

Table 14.1 Summary of communication processes across different dyadic coping models

Theoretical perspective	What each partner does to cope with his or her own stress	What one partner does to communicate that he/she is stressed to the other	What one partner does to help the other partner cope with stress				What partners do together to cope with stress (often common stressors)	
			Positive support		Negative support	No support		
			Emotion-focused	Problem focused			Emotion-focused	Problem-focused
Relationship-focused coping (Coyne and Smith [125])		Active engagement	Active engagement Protective buffering	Active engagement	Protective buffering Overprotection			
Coping Congruence (Revenson [100])	Congruence		Congruence	Congruence	Incongruence			
Systemic-Transactional (Bodenmann [104])		Stress communication	Supportive dyadic coping	Supportive dyadic coping Delegated dyadic coping	Negative dyadic coping (ambivalent, superficial, hostile)		Common dyadic coping	Common dyadic coping
Relational-cultural model (Kayser et al. [98], Kayser and Scott [134])					Disengaged avoidance		Mutual responsivenesss	Mutual responsivenss
Relationship intimacy (Manne and Badr [135])		Reciprocal Self-disclosure	Partner responsiveness		Avoidance Criticism Pressure-withdraw		Relationship engagement Mutual constructive communication	Relationship engagement Mutual constructive communication
Developmental-contextual models (Berg and Upchurch [22])					Control coping Uninvolved coping		Collaborative coping	Collaborative coping

Note: Blank spaces indicate topic is not addressed.

have investigated the efficacy of couple-based interventions overall and for specific cancer types on psychological distress, quality of life, and communication within couples [145, 146].

The perspective that problems in coping may arise because of some problem in a relationship a patient is involved in has several implications. First, it is essential that health care professionals are aware and acknowledge that a unique sources or stress can be exacerbated or maintained by a interdependence among coping with the disease and influence of a partner [38, 144]. Second, it suggests a need to identify patients and partners at risk of ongoing distress [134]. Despite a significant push to integrate routine screening of [147], the relationship between screening for distress among patients and partners and improvements in psychosocial outcomes is unclear. Carlson and colleagues found that breast and lung cancer patients who meet threshold for distress and were referred to psychosocial services were less likely to have high distress at follow-up than those that received minimal screening with referral [148]. Fielding and Lam [149] suggest that attempts to screen all patients for distress will yield a significant number of false-positives, potentially resulting in provision of clinical services for people who do not need them, increasing clinical and financial burden on health services [150]. A more personalized and nuanced approach to identification of distress among patients and partners by clinicians involved in routine care has been suggested as a more cost-effective alternative in the long-run [151, 152].

There is research that also suggests that many patients that are screened and identified as being distressed do not receive appropriate psychosocial care [153]. Moreover, rates of self-reported need for structured psychosocial care have been observed as ranging from 20% to 66% for patients with breast, prostate, hematologic, and gastrointestinal cancer [154, 155], and approximately 25% for partners of patients with breast, lung, hematologic, and gastrointestinal cancer [156, 157]. Ellis and colleagues [158] identified greater depressive symptoms, being unmarried, and younger age as being significant predictors of acceptance of psychosocial support referral among patients with lung and gastrointestinal cancer.

This is consistent with a study undertaken by Merckaert and colleagues, who observed predictors of acceptance of psychosocial support among partners of patients with breast, hematologic, and gastrointestinal cancer included being younger age, increased distress, and being partners with a patient who also desired psychosocial support. Taken together, these data suggest screening alone is insufficient for identifying, referring and treating patients and partners who are distressed. Several strategies have been proposed to enhance the impact of psychosocial distress screening for patients and partners within routine care, including psychoeducation about the impact of distress and the cancer journey with screening results [157, 159], and training clinicians to engage meaningfully with patients and partners about emotional issues in the context of cancer [153]. There is some qualitative evidence to suggest that addressing the emotional needs of partners within routine care falls outside the role of oncology clinicians [160]. Table 14.2 outlines a five-step process recommended by the American Psychosocial Oncology Society [161] to improve screening, referral and follow-up of patients at risk of being impacted by increased psychosocial distress resulting from their experience with cancer. These recommendations have been amended in Table 14.2 to included consideration for the distress of partners. These steps can be thought of as minimum requirements when considering how clinicians or clinical services might consider implementing psychosocial screening. They should not be considered as "one size fits all" approach to how best to support people experiencing distress in the context of cancer.

14.5.1 Counseling for Cancer Survivors and Partners

Greater acknowledgement of the interdependence of patients and partner responses to cancer has been reflected by notable growth in research in interventions being designed, implemented and evaluated that target both the patient and

Table 14.2 Possible adaptation of APOS process for including partners in screening activities

Step 1: Screening	Step 2: Evaluating	Step 3: Referring	Step 4: Following-up	Step 5: Documenting & quality improvement
Initial screener for patients and partners: National Comprehensive Cancer Network-Distress Thermometer (NCCN-DT)	NCCN-DT Cut-off scores ≥4 [162], administer more in-depth evaluation. Administration of more in-depth psychometric measure e.g., Personal Health Questionnaire-9 (PHQ-9; [163])	Patients or partners with moderate levels of distress should be considered for referral to mental health services, social work, chaplaincy within 1–3 days [148]. Discuss this with persons first, educate on role of these services, and ensure additional support wanted at time before referring.	Primary care team should follow-up with persons who have been referred, in a timely fashion. Monitor those who have declined referral wherever possible. Keep patients and partners or family caregivers 'in the loop' regarding available services.	Document all instances of screening and referral, include partner screening with patient screening if appropriate. Identify areas for improvement in screening, referral and follow-up processes. Seek feedback from patients and partners.

their partner [145, 146]. A number of meta-analyses have been undertaken demonstrating moderate effects of psychosocial interventions for those with cancer on a range of outcomes, including anxiety, depression, and quality of life [164–170]. Partners of people with cancer often describe similar reactions to a cancer diagnosis, including shock [171–173], distress [173–175], anxiety [171, 172, 176], depression [171, 172, 176], fear and uncertainty [134, 171, 172], and denial [171].

Moreover, since evidence exits that indicts that partner or caregiver anxiety may be associated with patient anxiety, and may influence other illness adjustment outcomes including depression, fatigue, and symptom management [176] it is logical to consider these relationships in the development and implementation of various intervention approaches. However, interventions directed solely at partners or caregivers have been shown to have low to moderate effects on anxiety, sexuality, and relationship satisfaction [177–179]. Given the prevalence of psychological distress among patients and their partners there has been a modest but increasing trend towards interventions that improve adjustment for both patients and partners ("couple-based" interventions) following a cancer diagnosis and treatment. Aside from the benefits to patients' and partners' psychological and physical well-being [144, 164, 180], there are also significant health care cost-benefits for intervening with distressed individuals [181–183]. There have been several meta-analyses and reviews of psychosocial interventions designed for patients diagnosed with cancer and their partners [164–170, 177–180, 184–187].

Overall, interventions designed for couples also show small to moderate effect sizes on a number of outcomes, most notably relationship-based outcomes (e.g., relationship satisfaction), psychological outcomes (e.g., anxiety, depression), and communication within couples [145, 146]. A systematic review undertaken by Regan and colleagues explored the impact of couple-based interventions across a number of common clinical outcomes. Nine of 18 studies that assessed psychological distress (conceptualized as including anxiety, worry, agitation, depression, sadness, mood disturbance) as an outcome, only six of 18 studies that assessed this for patients reported significant improvements compared to treatment at the final follow-up point of the intervention [188–193]. For partners, only two studies reported significant improvements compared to treatment as usual at final follow-up [188, 189].

On sexuality outcomes, two of five studies that assessed self reported outcomes reported significant improvements at final follow-up for

patients compared to controls [191, 193], and only one study reported improvements for partners [191]. On relationship functioning (i.e., satisfaction with relationship; perceived quality of the relationship), four of nine studies reported significant improvements compared to controls at final follow-up for patients and partners [189–191, 194]. On measures of communication, two of five studies reported improvements for patients immediately after the intervention had finished [193, 195], and one study reported improvements for partners at 3-month follow-up [195]. Coping strategies improved in two of five studies for both patients and partners at the final follow-up point [193, 196]. Despite consistent evidence for the role of interpersonal factors on various outcomes in cancer survivors it appears that at this time only moderate success across a range of psychosocial outcomes, are currently achieved following delivery of couple-based interventions.

14.5.2 Why has it Been So Difficult to Initiate Couples Counseling in Cancer Survivors?

Studies exploring patients' and partners' perspectives regarding psychosocial care provision in general indicate that partners are generally less satisfied than patients with the care received [197–200]. Partners' dissatisfaction relates to a view that they are often left feeling unsure or confused regarding cancer treatment, particularly regarding the physical and emotional side effects of the treatment, [198–200]. Partners' also tend to report a lack of sensitivity and understanding regarding the breadth of patients' and partners' psychosocial issues (i.e., beyond emotional impacts) [197, 200], and a lack of clear support pathways for themselves and other family members [197–199]. Given partners of patients and family members are most often key caregivers for patients [201], and often report greater levels of unmet needs [201, 202], and anxiety [203, 204] than patients.

Several studies have shown that health care providers (HCPs) attitudes toward psychosocial care for patients and partners with cancer are a salient barrier [197, 205–210]. Despite the push from many international clinical practices guidelines encouraging HCPs to use specific distress screening tools [175, 211], HCPs have reported inconsistent views regarding the importance, feasibility, and effectiveness of identifying and addressing psychosocial issues [205, 207, 209] and who should provide psychosocial support [206]. Discrepancies also exist between HCPs and couples [207, 208, 212, 213]. For example, compared to patients and partners, HCPs underestimate couples' psychosocial needs [207], communication and spirituality needs [213], sexuality needs [212], and patients' ability to manage the stress of cancer [208].

Consistent with previous research [214, 215], both patients and partners report that they were more likely to accept or seek out some type of psychosocial support when the recommendation was made by an oncologist or surgeon rather than some other health care professional. The support of a HCP when problems within the dyad are present is very important. As the reviews indicate there is some support for the effectiveness of these interventions. There is no reason for lack of referral if a risk-based evaluation indicates problems within the dyad that seems to be interfering with long term adaptation or high levels of distress.

14.6 Future Directions

The emergence of a dyadic view of the stress cancer survivors and their partners experience as a result of their encounter with a life threatening illness and the resulting joint coping efforts required has been transformative for researchers interested in the study of close relationships and coping in the context of health. This effort provides a unique shift in the focus of attention from the individual patient to the dyad. Despite the advances made in the last decade due to new methodologies and novel frameworks as it related

the cancer patient, survivor and dyad, significant work remains translating these finding into highly effective interventions delivered to survivors and partners where appropriate.

Future work needs to be aimed at increased understanding at a deeper or mechanistic level of the role of dyadic coping on outcomes of many types of chronic illnesses over the life-span [100]. We need to expand our ability to integrate multiple levels of dyadic relationship analysis at some minimal skill level in the daily practice of cancer survivor care. While current knowledge in this area is based on existing research of mostly heterosexual, middle-aged, Caucasian participants from Western industrialized countries [39] there has been some recent explorations of couples coping with stress from a cross-cultural perspective [216] and within same-sex relationships [217].

Similar work should be conducted to provide culture and norm specific information related to cancer. Kayser and colleagues [218] illustrate such a possibility in their research comparing couples coping with breast cancer from USA, India and China. Research regarding the psychosocial impact of cancer among same-sex couples is limited. Research by Aizer and colleagues suggests intimate relationships might be associated with increased survivorship in heterosexual relationships by way of access to better healthcare among married patients, decreased psychological distress and better adherence to treatment compared to unmarried patients [219]. Research among breast cancer patients with a same-sex partner suggests an association between disclosure of orientation and decreased psychological distress [220]. These data indicate that there are possible differences between the experience of heterosexual and same-sex couples when it comes to their experience and receipt of cancer care. Future research regarding intimate relationships within the cancer survivorship context should aim to be more inclusive of same-sex relationships.

While evidence exists for a low-moderate effect for couple-based interventions for cancer survivors, on communication, sexuality, and quality of life [39, 145], approaches need to be made more robust. Additional research is needed to understand which couples benefit more from this form of intervention, what is the optimal format and length for its delivery, and its cost-effectiveness [40]. There is still the need to better understand how these interventions should be delivered, including identification of effective components of these approaches, when to implement in the cancer experience and what dimensions of interactions should be targeted [145, 146]. Direct translation of interactional processes observed within couples facing health crises may provide information to better tailor intervention to help modify these processes again in the context of a health challenge. Similarly, it will be important to investigate the role of possible moderators of treatment efficacy (i.e. treatment, stage of the disease, length of relationship, gender, culture, and attachment style), the use of new media and the clear identification of the ultimate goal of the intervention [221].

Despite the modest outcomes related to the use of interpersonal based interventions [62, 82, 145, 146] at present, the evidence highlights the importance of interpersonal influences on outcomes related to cancer survivorship, suggest that more translational research aimed at elucidating the role of interpersonal factors on specific outcomes and interventions to modify these processes in patients and their partners is justified. As this chapter indicates, there is currently an abundance of theory but modest evidence for the potential role of interventions directed at modifying interpersonal factors.

14.7 Conclusion

Despite ongoing efforts to improve communication skills in all facets of oncology [222], addressing the patient-partner role in achieving optimal outcomes can be complex and multi-faceted. Greater clarity regarding the common barriers and delineating specific elements of interactions that underlies problems that patients and partners face at an individual, dyadic, and systems level has the potential to improve patient care. While interventions to help patients and partners more effectively cope with the challenges of living fol-

lowing diagnosis and treatment of cancer demonstrate a modest degree of efficacy across a range of outcomes, the effectiveness of these approaches need to be more consistent and improved overall. Also on a practical note, these interventions remain difficult to implement for researchers, clinicians and often difficult to access by cancer survivors and most likely need to be simplified. Health care professionals often acknowledge the extent of psychosocial distress within interpersonal relationships but currently lack the conceptual basis for understanding these interactions and often lack the training to adequately address the interactional nature of coping with illness.

Understanding the theories of interpersonal interactions that help us appreciate the role that partners can often play in optimizing the long-term health and well-being of cancer survivors is necessary but not sufficient to improve outcomes. As most experienced clinicians know it is also the time, patience and know how to potentiate this support system that can make all the difference between ongoing problems and a reasonable therapeutic partnership among provider, patient and spouse or partner. Greater attention to developing and evaluating efforts to efficiently and more effectively impact the role of constructive relationships among cancer survivors, spouses/partners and clinicians of all types, represents a relatively untapped area by mainstream cancer survivorship research with potential to improve future long term outcomes in this group.

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Part V

Problem Area: Lifestyle

Physical Activity

15

Laura Q. Rogers, Stephen J. Carter, Grant Williams, and Kerry S. Courneya

15.1 Concepts and Definitions Relevant to Physical Activity and Exercise

Several concepts and definitions are important for accurately interpreting and translating scientific literature into cancer survivorship care. Although the terms "physical activity" and "exercise" are often used interchangeably, nuanced differences between these descriptors exist, especially in the field of kinesiology. Body movement caused by muscle action that increases energy expenditure is considered "physical activity," while the term "exercise" is used when the movement is planned, purposeful, and structured [1]. Moreover, the term "fitness" is typically used to represent cardiorespiratory (aerobic) fitness when, in fact, physical fitness encompasses multiple aspects related to one's ability to perform physical activity (e.g., cardiovascular endurance, muscle endurance, muscle strength, flexibility, and body composition) [1]. Given the variability in the extent to which exercise training was strictly controlled in prior exercise and cancer intervention studies and the frequent use of more general measures of physical activity in observational studies, the more inclusive term of "physical activity" is used here unless specifically referring to exercise training studies (Table 15.1).

15.2 Prevalence of Physical Activity Among Cancer Survivors and Trajectory After Diagnosis

15.2.1 Cancer Survivor Participation in Aerobic Physical Activity and/or Strength Training

Cancer survivors are at risk for reduced physical activity post-diagnosis and are more likely to report less physical activity when compared with non-cancer groups. In the USA (National Health Interview Survey), only 33% of cancer survivors meet aerobic physical activity recommendations of ≥150 weekly minutes of moderate-to-vigorous physical activity [6]. This prevalence differs between countries as exemplified by 45% of Norwegian cancer survivors [7] and 27% of Canadian cancer survivors self-reporting meet-

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Table 15.1 Physical activity and exercise study designs: a terminology continuum

	Observational studies (prospective, case-control, etc.)	Behavior change intervention studies	Exercise training studies
Study intervention	None	Asked to increase movement using specific exercise recommendations and/or integration into activities of daily living; provided behavioral support; exercise usually unsupervised and not tightly controlled	Given specific exercise prescription with exercise sessions tightly controlled and primarily supervised; behavioral support may be provided to enhance adherence
Activity-related measurement examples	Self-report, accelerometer, pedometer	Self-report, accelerometer, pedometer	Session adherence and attendance records
Recommended terminology	Physical activity	Physical activity	Exercise
Study example	Relationship with cancer outcomes (e.g., mortality, recurrence) [2, 3]	Effects of a telephone-based intervention on physical activity in breast cancer survivors [4]	Effects of a specific supervised exercise regimen on quality of life in lymphoma cancer survivors [5]

ing aerobic physical activity recommendations [8]. Based on the US Behavioral Risk Factor Surveillance System (BRFSS), cancer survivors are more likely to report physical *in*activity when compared with respondents without a history of cancer (odds ratio of 1.11 with 95% confidence interval [CI] of 1.07–1.15) [9]. Also, the prevalence of physical activity varies based on cancer type as represented by the American Cancer Society's Study of Cancer Survivors (SCS)-II survey of individuals with 6 different cancer types (e.g., uterine cancer survivors being least physically active [29.6% meeting recommendations] and individuals with a history of skin melanoma being most physically active [47.3% meeting recommendations]) [10]. Levels of physical activity may be even lower in cancer survivors with a history of understudied, less prevalent cancer type (e.g., only 8.5% of head and neck cancer survivors reported meeting aerobic physical activity recommendations) [11].

Prevalence of participating in strength training is also suboptimal as demonstrated by 23% of Canadian cancer survivors reporting meeting strength training recommendations [12]. Data from the US Health Information National Trends Survey (HINTS) found that 24% of women with history of breast cancer and 16% of all other women cancer survivors self-reported engaging in strength training 2 or more days per week [13]. Women cancer survivors with a cancer type other than breast were 30% less likely to report meeting strength training guidelines (odds ratio of 0.70 with 95% CI of 0.51–0.96) [13]. In contrast, a third of US men regardless of history of cancer reported meeting strength training recommendations [13]. Irrespective of gender or cancer type, ≤ 20% were meeting both aerobic and strength training recommendations [13]. This is similar to the 12.3% reported in Australia among prostate cancer survivors and 22% reported in Canada among hematologic cancer survivors [14, 15]. Little is known about how meeting aerobic only, strength training only, or both aspects of the recommendations may differ with regard to prevalence, correlates, and predictors. As such, future research on prevalence and related factors should differentiate between and report on meeting recommendations for aerobic exercise only vs. strength training only vs. both aerobic and strength training [15, 16].

15.2.2 Physical Activity Trajectory After a Cancer Diagnosis

A decline in physical activity is typically seen in the months to years following cancer diagnosis. Among breast cancer survivors, the volume of self-reported physical activity decreased in the 12 months after diagnosis (i.e., 18.8 metabolic

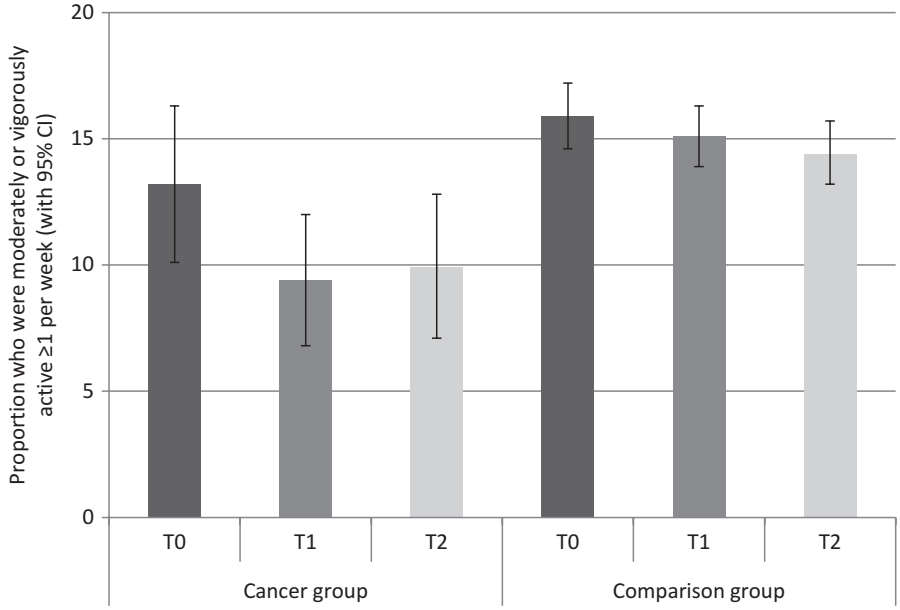

Fig. 15.1 The proportion of individuals age≥50 years who were moderately or vigorously active at least once per week at each time point: cancer survivors vs. those without a history of cancer (T0 = 0–2 years before cancer diagnosis, T1 = 0–2 years after cancer diagnosis, and T2 = 2–4 years after cancer diagnosis; proportions adjusted for age, sex and wealth). (From Williams et al. [20]. With permission)

equivalent [MET]-hours/week pre-diagnosis and 9.2 in the year post-diagnosis) [17]. Although this rebounded in the years that followed (15.0 MET-hours/week at 19–30 months post-diagnosis), the increase did not return to pre-diagnosis levels [17]. Consistent with the positive association between pre-diagnosis and post-diagnosis physical activity previously reported in the literature [18], 48% of the cancer survivors (mixed cancer types) meeting physical activity guidelines pre-diagnosis continued to meet recommendations post-diagnosis even after the potentially life-altering event, that is, a cancer diagnosis [8]. However, individual variability exists as exemplified by 19% of cancer survivors not meeting recommendations pre-diagnosis increasing their physical activity to meet recommendations post-diagnosis [8].

Older cancer survivors are at greater risk of failing to maintain or increase physical activity post-diagnosis, as late-age cancer diagnosis increases the risk of functional impairment [8, 19]. In the UK, a prospective cohort study of older adults revealed that the age-related decline in physical activity (self-reported engaging in moderate-to-vigorous physical activity at least once a week) was exacerbated by a cancer diagnosis (mixed cancer types; 13.2% pre-diagnosis decreased to 9.9% post-diagnosis with the decline in the non-cancer group over the same time period being 15.9% to 14.4%) (Fig. 15.1) [20].

15.3 Physical Activity Benefits and Potential Mechanisms

15.3.1 Importance of Physical Activity for Health and Well-Being of Cancer Survivors

Physical activity provides multiple biopsychosocial benefits, and cancer survivors should be encouraged to engage in regular physical activity as a means to improve health and well-being [21]. Physical activity benefits include but are not limited to increased muscle strength/endurance and cardiorespiratory fitness along with favorable changes in body composition and physical functioning [22]. Short- and long-term effects of cancer and its treatment, such as fatigue, poor sleep quality, and reduced health-related quality of life, can be

attenuated by regular physical activity [23–25]. Importantly, physical activity can improve biomarkers of health such as reduced systemic inflammation, increased insulin sensitivity, decreased estrogens/androgens, and reduced central adiposity [26–32]. Therefore, current guidelines recommend that cancer survivors perform at least 150 min per week of moderate intensity aerobic physical activity and twice weekly strengthening exercise (Table 15.2) [33, 34].

Table 15.2 Physical activity recommendations for cancer survivors with application to evidence-based exercise prescription [33–36]

Recommendation component	Training variable	Suggested prescription	Comments
Aerobic: 150 min per week of moderate intensity physical activity (≥ 10 min bouts; 1 min of vigorous equates to 2 min of moderate)	Frequency	3–5 days/week	At least 3 days/week is recommended
	Intensity	55/65–90% of VO2max 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 min/day	Exercise may be completed in smaller exercise bouts of ≥10 min throughout the day
	Type	Large muscle groups involving, continuous rhythmic activity	Pick an enjoyable activity
Strength training: 2 to 3 weekly sessions that include major muscle groups (not on consecutive days)	Frequency	2–3 days/week	≥ 48 h should be allowed between workouts of the same muscle group
	Intensity	MS: > 60% of the 1RM ME: < 50% of the 1RM 16 RPE (prior to failure) or 19–20 RPE (point of fatigue) on last repetition	40–50% of the 1RM for older novice exercisers. 60–70% of the 1RM for novice to intermediate exercisers. ≥ 80% of the 1RM for experienced strength trainers
	Repetitions	2–4 sets of 8–12 repetitions (MS, 3–8 repetitions; ME, 15–20 repetitions)	Rest intervals of 2–3 min between sets are recommended
	Type	Resistance exercises targeting each major muscle group	Should include core/stabilizing exercises in addition to upper and lower body exercises
Flexibility: Stretch major muscle-tendon groups on days when other exercises are performed	Frequency	On days aerobic and/or strength training exercises are performed (preferably most days per week)	Can be included in the warm-up and cool-down phases of every workout to support ROM
	Intensity	The muscle/joint should be stretched to a point of feeling tightness or slight discomfort	Stretching to the point of pain is not advised
	Duration	10–30 s/stretch 2–4 times/stretch	Holding a stretch for 30–60 s may confer greater benefit in older persons
	Type	Slow and controlled static stretching for all major muscle groups	Tailor stretches to physical limitations if necessary

See Table 15.4 for potential tailoring based on cancer-specific needs and barriers

Key: *HRR* heart rate reserve, *VO2max* maximal oxygen consumption, *HRmax* maximum heart rate, *RPE* rating of perceived exertion [10–24], *MS* muscular strength, *ME* muscular endurance, *1RM* one-repetition maximum, *ROM* range of motion

15.3.2 Potential Underlying Mechanisms for Physical Activity Benefits

Several mechanisms are believed to be responsible for physical activity's beneficial effects on health. These mechanisms are supported by substantial research and occur directly or indirectly through the effects of physical activity on adiposity and skeletal muscle [26–28, 37, 38]. These mechanisms include beneficial effects on sex hormones, insulin axis, adipokines, and inflammation [37, 38]. Potential yet less well-studied mechanisms include the effects of physical activity on immune function, autonomic nervous system modulation, antioxidant enzyme systems, gut microbiota composition, and epigenetic processes [38–43].

15.4 Exercise and Physical Activity After Cancer

15.4.1 Post-Diagnosis Physical Activity and Cancer Risk

Relative to cancer outcomes, multiple prospective observational studies have reported the associations between physical activity and cancer recurrence and/or mortality with most studies focusing on breast, colorectal, prostate, or gynecologic cancers [44–46]. A recent meta-analysis found that pre- and post-diagnosis physical activity is associated with reduced cancer mortality among cancer survivors (all cancer types combined) [46]. Importantly, the reduction in risk is greatest with physical activity reported after a cancer diagnosis indicating that the "teachable moment" of a cancer diagnosis for improving healthy lifestyles does not come too late for risk reduction to occur [46, 47]. More physically active breast and colorectal cancer survivors post-diagnosis were 28% (relative risk = 0.72, 95% CI 0.60–0.85) and 26% (relative risk = 0.74, 95% CI 0.58–0.95) *less* likely to die from their cancer, respectively [2, 3]. Although the reduction in risk after prostate cancer is also likely, this relationship has been less consistent than that for breast and colorectal cancer [48]. Furthermore, limited data exist for other cancer types. Generalizing data across cancer types should not be done given the variability in associations between physical activity and cancer incidence including potential increased risk for cancer types such as malignant melanoma [49]. While cancer outcomes such as recurrence and mortality are of high priority, exercise and physical activity after cancer treatment may prevent, reverse, and/or attenuate symptoms that negatively impact quality of life (e.g., fatigue, etc.) in many cancer survivors.

15.4.2 Early Intervention May Enhance Ability to Engage in Physical Activity After Cancer Treatment

While this chapter focused on the effect of exercise for cancer survivors who have completed treatment (surgery, chemotherapy, and/or radiation), exercise training before cancer surgery may increase the cancer survivor's ability to engage in and benefit from regular physical activity after cancer treatment. The majority of prehabilitation (e.g., presurgery) studies testing physical exercise training have enrolled patients with lung cancer awaiting resection or cancers requiring abdominal surgery; these data strongly suggest that aerobic and/or resistance exercise presurgery can improve functional walking capacity (e.g., 6 min walk test), increase cardiorespiratory fitness, and/or reduce hospital length of stay [50]. These benefits are exemplified by a meta-analysis of seven randomized presurgery exercise trials in lung cancer patients; the mean difference in hospital length of stay was −4.83 days for presurgery exercise vs. control with presurgery exercise reducing the risk of pulmonary complications by 45% (risk ratio = 0.55, 95% CI 0.34–0.89) and all complications by 55% (risk ratio = 0.45, 95% CI 0.28–0.73) [51]. Data regarding prehabilitation in patients with cancers other than lung remain limited, and further research with larger randomized controlled trials that also measure effects on longer-term physical

activity behavior (after cancer treatment) is needed [50]. Similarly, a multitude of randomized controlled trials have reported exercise benefits during cancer treatment (chemotherapy and/or radiation) that may increase the cancer survivor's ability to engage in physical activity posttreatment (e.g., better physical functioning and cardiorespiratory fitness) [21, 22, 24].

15.4.3 Rehabilitation After Completion of Cancer Treatment

Numerous randomized controlled trials have reported physical activity benefits after completion of cancer treatment [21–23]. The magnitude of physical activity intervention effects is greater in the posttreatment period, especially when initiated sooner rather than later [32, 52]. Also, data suggest that delaying initiation of exercise training until posttreatment may not negatively impact response to exercise and cancer survivors who have recovered sufficiently from primary treatment may be better able to adhere and thus achieve/tolerate a higher exercise dose [53]. Well-studied physical activity benefits posttreatment include improvements in cardiorespiratory fitness, muscle strength, physical functioning (objective and self-report), body composition, bone health, fatigue, body image/self-esteem, emotional well-being, social functioning, anxiety, and quality of life [21–24, 54–59]. Self-reported sleep quality may also improve with physical activity [23, 25, 60]. Although less well-studied, physical activity provides important benefits in advanced cancer patients including improved functional mobility, longer maintenance of independent function, attenuated declines in quality of life, and reduced fatigue [61]. Even less is known about the safety and benefits of exercise training for treatment of cachexia [62, 63]. Until further research is available, it is recommended that exercise be considered a potential component of multimodal interventions in cachectic patients (e.g., combined with nutritional and/or pharmacologic agents) rather than a single modality approach [62].

15.4.4 Physical Activity Risks

Physical activity is generally considered safe and well-tolerated as demonstrated by the lack of related adverse events in the majority of randomized trials reporting on these outcomes [23, 24, 64, 65]. When reported, adverse events are typical of that expected in a non-cancer population (e.g., musculoskeletal complaints, soft tissue injury from exercise, or unmasking of a cardiac condition) [23, 24, 66]. It is now widely accepted that resistance exercise does not increase risk of upper extremity lymphedema in breast cancer survivors, yet little is known about the effects of exercise on lower extremity lymphedema or lymphedema in patients with cancers other than breast [67]. However, individuals with lymphedema should wear a compression garment during resistance sessions, consider exercise professional assistance to ensure proper resistance exercise form, and seek attention from their physician or lymphedema specialist if lymphedema symptoms worsen [34, 68, 69].

15.4.5 Scientific Knowledge Gaps

Very few randomized exercise training trials have reported long-term cancer outcomes related to recurrence and survival. While not powered to detect differences in survival, the START trial (Supervised Trial of Aerobic Versus Resistance Training) involving 242 breast cancer survivors during chemotherapy did conduct a secondary analysis after a median follow-up of 8 years. It was noted that disease-free survival was 82.7% in the exercise groups vs. 75.6% in the control group (hazard ratio = 0.68, 95% CI 0.37–1.24) [70]. Although limited, these findings are consistent with observational studies suggesting potential long-term improvements in cancer outcomes with physical activity. At least two randomized exercise trials specifically focusing on cancer outcomes are ongoing. First, CHALLENGE (Colon Health and Life-Long Exercise Change) is investigating exercise effects on disease-free survival in high-risk stage II and III colon cancer patients who have

recently completed chemotherapy [71]. Also, INTERVAL (Intense Exercise for Survival) is investigating the effects of an intense exercise program on overall survival in men with metastatic castration-resistant prostate cancer [72, 73]. While these ongoing studies will address important questions about the effects of exercise training on cancer outcomes such as survival, exercise and physical activity can assist the cancer survivor with other important survivorship needs related to rehabilitation after cancer treatment.

With regard to these rehabilitation-related outcomes (e.g., physical functioning, quality of life, etc.), most prior randomized trials have enrolled cancer survivors with breast, colorectal, prostate, head and neck, gynecologic, hematologic, or mixed cancer types and focused on during treatment, posttreatment, or both [23, 24, 74]. Other cancer types such as multiple myeloma and bladder, among others, remain understudied [75, 76]. Similarly, data regarding physical activity benefits in children and young adults during and after childhood cancer are limited and inconsistent [65, 77, 78]. Furthermore, racial minorities have been underrepresented in physical activity research in cancer survivors [79, 80]. Also, as older adults with cancer represent the majority of new cancer diagnoses, physical activity and exercise training interventions tailored to this vulnerable and growing population are warranted. In addition to these subgroups, limited data are currently available regarding the effects of physical activity and/or exercise training on understudied comorbidities and symptoms. For example, great interest exists in better elucidating aerobic exercise training as a means to alleviate the cardiotoxic effects of chemotherapy [81]. Physical activity has demonstrated promise related to improved cognitive function in cancer survivors, but additional research is needed [82, 83]. Also, little is known about physical activity and exercise training effects on several understudied symptoms such as arthralgias related to antiestrogen therapy, peripheral neuropathy, and pain [23, 24, 84]. Finally, individual (e.g., demographic) and cancer-related factors may influence a cancer survivor's response to physical activity, yet little is known about how to tailor physical activity interventions on these factors for optimal benefit [85–89]. Nevertheless, the current state-of-the science supports the importance of physical activity and/or exercise training as a fundamental aspect of cancer survivorship care.

15.5 Physical Activity and the Caregiver

Maintaining the health and well-being of the cancer survivor's caregiver is essential to optimizing the cancer survivor's ability to cope with, navigate through, and recover from the cancer experience. During the 5 years after the cancer diagnosis, 22% of caregivers suffered a decline in physical functioning and 30% were below the population norm for physical functioning at the end of the 5 years [90]. The most common physical symptoms reported by caregivers include fatigue (37%), anxiety or fear (37%), difficulty sleeping (30%), and weight gain (24%) with such symptoms being potentially responsive to physical activity interventions [91].

Engaging caregivers along with the cancer survivor in structured physical activity and nutrition programs assists the caregivers in "sharing the journey" with their loved one, improves caregiver health and well-being, and facilitates social support for the cancer survivor [92]. Moreover, social support such as that provided by caregivers can play an important role in increasing physical activity adherence by the cancer survivor [93–95]. Several studies have reported physical activity intervention benefits when a caregiver or significant other is included, and Kamen et al. [96] reported enhanced benefits on outcomes such as depression when a dyadic rather than individual intervention is used [96–98]. Therefore, future research and public health interventions should consider the well-being of both the caregiver and cancer survivor in an effort to optimize intervention benefits.

15.6 Using Health Behavior Theory to Help Cancer Survivors Adopt a More Physically Active Lifestyle

15.6.1 Physical Activity Behavior Change Interventions for Cancer Survivors

Exercise-related interventions can be tested in health outcome trials (i.e., primary outcome is a health or psychosocial outcome) or behavior change trials (i.e., primary outcome is exercise or physical activity adherence) [99]. Although the distinction may, at times, be difficult to discern, several reviews have attempted to focus specifically on randomized trials testing intervention effects on physical activity behavior. A 2013 Cochrane review compared 14 randomized controlled trials testing a physical activity behavior change intervention vs. usual care in adults with homogenous primary cancer diagnosis [100]. The interventions most beneficial in increasing physical activity behavior shared the following characteristics: (1) set a specific program goal, (2) generalized the target behavior (participants asked to engage in physical activity outside the immediate intervention environment), (3) encouraged self-monitoring of exercise behavior, and (4) prompted practice [100, 101]. Although the standardized mean difference indicated improvements in aerobic exercise tolerance, no intervention reported 75% or more of participants were meeting physical activity recommendations post-intervention. Most trials enrolled breast cancer survivors, and few focused on ethnic minorities. Almost all focused on aerobic exercise with inclusion of resistance training being less frequent. Stacey et al. [102] also confirmed that most prior behavior change trials have enrolled breast cancer survivors and used a variety of intervention delivery methods. The standardized mean difference (i.e., 0.33) for this meta-analysis also supported increases in physical activity with the interventions tested, yet a particular delivery method did not stand out as being most effective [102]. Goode et al. [103] reviewed behavior change interventions for cancer survivors using the delivery methods of telephone, print, or web-based strategies to improve physical activity, diet, or weight management. Most trials enrolled breast cancer survivors and most interventions initiated behavior change. Notably, few trials reported information concerning maintenance and fewer still reported cost-effectiveness [103].

15.6.2 Behavior Change and Technology

Technology-based delivery methods are increasingly being integrated into physical activity behavior change interventions for cancer survivors, especially among cancer survivors with a history of childhood, adolescent, or young adult cancer [104]. Published randomized controlled trials of technology-supported physical activity behavior change interventions enrolling cancer survivors have used a variety of approaches (e.g., web-based modules, social media platforms, email and/or text messaging, access to trained staff, videoconference, self-monitoring) [105–109]. Sample sizes for all but one randomized controlled trial have ranged from 18 to 86. Only two reported a statistically significant intervention effect on physical activity, yet no objective physical activity measure was reported, final assessment was at 3 months, and only one was in the USA [107, 109].

Single-arm studies reporting interventions (e.g., pedometer-based computer-tailored, online activity tracking with email updates, text messaging + telephone counseling) have not reported statistically significant increases in physical activity [110–112]. In the three US randomized controlled trials, minority representation was ≤9%, and cost-effectiveness was not reported. To date, randomized controlled trials of web-based interventions have not tested efficacy with an objective physical activity measure nor have interventions targeted a diverse sample of cancer survivors with special attention given to the unique needs of subpopulations such as older and underserved cancer survivors. Technology holds great promise for increasing access to behavior change interventions, and further research is

needed to determine best practices for increasing the magnitude of behavior change achievable with technology-based interventions.

15.6.3 Longer-Term Adherence

Among the multiple behavior change interventions tested in cancer survivors, few have documented continued statistically significant intervention effects on physical activity months after intervention completion [4, 66, 113–117]. Of these studies, only three have documented persistent statistically significant intervention effects with objective physical activity monitoring devices (i.e., accelerometer or sealed step counter) [66, 114, 116]. Rogers et al. [66] tested a multicomponent intervention entitled Better Exercise Adherence after Treatment for Cancer (BEAT Cancer) targeting postprimary cancer treatment breast cancer survivors. This intervention included six discussion/education group sessions and supervised exercise sessions that tapered to unsupervised home-based exercise with update counseling support (Table 15.3). The odds of engaging in at least 150 weekly minutes of moderate-to-vigorous physical activity was significantly higher in BEAT Cancer participants at 3 months (immediately post-intervention) and 6 months (accelerometer month 3 [M3] adjusted odds ratio = 2.2; 95% CI = 1.0–4.8 and month 6 [M6] adjusted odds ratio = 2.4; 95% CI = 1.1–5.3; self-report M3 adjusted odds ratio = 5.2; 95% CI = 2.6–10.4 and M6 adjusted odds ratio = 4.8; 95% CI = 2.3–10.0) [66]. Pinto et al. [116] tested a volunteer-led intervention for breast cancer survivors entitled Reach to Recovery. American Cancer Society volunteers were trained in the delivery of a 12-week coaching intervention. Although the odds of meeting recommendations based on self-report was significantly higher for the intervention participants at 12 weeks *only* (odds ratio = 13.1), the adjusted mean difference in accelerometer-measured moderate-to-vigorous physical activity favored the intervention group at both 12 weeks (mean difference = 48.5 weekly minutes, $p < 0.01$) and 24 weeks (mean difference = 38.7 weekly minutes, $p < 0.01$) [116]. James et al. [114] reported sealed pedometer results during testing of an 8-week diet and exercise weight loss intervention that included six theory-based group sessions, workbook, pedometer, and elastic tubing (Exercise and Nutrition Routine Improving Cancer Health [ENRICH] intervention). The adjusted mean difference in daily steps for ENRICH vs. wait-list control group was 2094.7 (95% CI 908.9–3280.5) at week 8 and 1761.0 (95% CI 184.3–3337.8) at week 20 [114].

Taken as a whole, longer-term adherence is infrequently reported and less frequently assessed with measures other than self-report. A variety of delivery methods have shown promise, but all have reported the same gradual attenuation of physical activity effects over time (a finding not unique to the cancer survivor population). Importantly, the attenuation of behavior change intervention benefits on health and psychosocial outcomes (e.g., fatigue, physical functioning, etc.) parallels the decline in physical activity further supporting the importance of addressing longer-term adherence in future studies [66, 83, 88, 118]. Strategies for enhancing longer-term adherence can be built into intervention design (e.g., instruction in barriers management [119], assisting individuals to adopt a physically active lifestyle mindset through cognitive reframing, increased self-efficacy, etc. [120, 121]) and continue after intervention completion (e.g., periodic booster sessions and/or follow-up telephone calls; ongoing technology-supported approaches such as text messaging [122] or continued use of social media group support [123]).

15.6.4 Health Behavior Theory

Health behavior theory is used for guiding intervention design and identifying the intervention aspects responsible for behavior change (i.e., "active ingredients") [124, 125]. To date, the theory of planned behavior, the social cognitive theory, and the transtheoretical model have been used most frequently in physical activity behavior change research among cancer survivors [124]. The few randomized trials reporting

Table 15.3 Elements of the Better Exercise Adherence after Treatment for Cancer (BEAT Cancer) physical activity behavior change intervention

	Number of sessions (content) for each week of the intervention			
Week	Discussion group session	Supervised exercise session	Unsupervised (e.g., home-based) exercise	Update counseling sessions
0	1 (intervention introduction; goal setting and journaling; exercise benefits, individualized behavioral modification strategies)	0	0	0
1	1 (time and stress management; goal setting and journaling; exercise logs reviewed; individualized behavioral modification strategies updated)	3 (education related to exercise prescription such as assessing intensity, overcoming barriers, setting goals, keeping exercise log, and avoiding injury; increased awareness of exercise benefits achieved; track progress and provide accountability)	0	0
2	1 (exercise barriers, benefits, and safety; journaling; exercise logs reviewed; individualized behavioral modification strategies updated)	3 (same as above)	0	0
3	0	2 (same as above)	≥2 (exercising on own and tracking progress with log builds self-efficacy)	0
4	1 (cancer survivor role model speaker)	2 (same as above)	≥2 (same as above)	0
5	0	1 (same as above)	≥3 (same as above)	0
6	1 (cognitive reframing; exercise barriers and relapse; journaling and exercise logs reviewed; individualized behavioral modification strategies updated)	1 (same as above)	≥3 (same as above)	
7	0	0	≥3 (same as above)	0
8	1 (wrap-up; relapse; journaling and exercise logs reviewed; individualized behavioral modification strategies updated)	0	≥3 (same as above)	1 (education related to exercise prescription such as assessing intensity, overcoming barriers, setting goals, keeping exercise log, and avoiding injury; increased awareness of exercise benefits achieved; track progress and provide accountability)
9	0	0	≥3 (same as above)	0
10	0	0	≥3 (same as above)	1 (same as above)
11	0	0	≥3 (same as above)	0
12	0	0	≥3 (same as above)	1 (same as above)

mediation testing (e.g., statistical methods used to determine which factors are responsible for an intervention's effect) have identified several important constructs responsible for intervention effects on physical activity behavior (e.g., intention to perform the behavior, planning for the behavior, perceived behavior control, barriers interference with the behavior, goal setting, social support, etc.) [126–130].Although self-efficacy (confidence) has not been confirmed as a mediating variable in a randomized trial in cancer survivors, it has been reported to significantly predict future physical activity behavior [131] and may be responsible for psychosocial benefits (e.g., quality-of-life improvements, reductions in fatigue) experienced with physical activity interventions [132, 133]. Self-efficacy can be measured for research purposes using published measurement tools [134, 135], while simple questioning can be used in practice for the purpose of guiding interventionist counseling and recommendations (e.g., How confident are you that you could exercise regularly? How confident are you that you could walk for 20 min at a moderately fast pace?). Also, personality traits (e.g., extraversion, conscientiousness) predict exercise adherence [136, 137], yet interventions that capitalize on these effects for optimal increases in exercise behavior have not been tested in cancer survivors. Moreover, promising health behavior theories that have been less well-studied related to physical activity behavior change in cancer survivors include self-determination theory (integrates autonomy) and attribution theory (integrates the individual's beliefs regarding why an outcome such as cancer occurred) [138–140].

15.7 Application

15.7.1 Practical Solutions

Translating the current state-of-the-art science regarding physical activity and related behavior change after a cancer diagnosis requires attention to barriers (especially those specific to cancer survivors) and strategies that target the effective intervention components identified, to date. With regard to barriers, greater symptom burden is associated with less physical activity in breast, colorectal, prostate, head and neck, and pancreatic cancer survivors and most likely other cancer types as well [47, 141, 142]. The symptom burden may be cancer-specific or comorbidity-related [143]. For example, one study found the top four exercise barriers among a mixed cancer survivor sample were illness/other health problems, joint stiffness, fatigue, and pain, all of which negatively influence physical activity [143]. Moreover, cancer survivors face typical motivational, time, and environmental barriers that are not cancer-specific [144, 145]. Table 15.4 provides coping and safety-related suggestions for dealing with the most common cancer-specific barriers. With regard to the most effective program elements, Table 15.5 summarizes key theoretical constructs, strategies for targeting these constructs, and related potential program elements.

15.7.2 Available Materials/Programs

An increasing number of investigators are making their evidence-based physical activity behavior change intervention materials available for broader use. For example, evidence-based programs can be found posted on the Research-Tested Intervention Programs (RTIPS) website hosted by the National Cancer Institute (https://rtips.cancer.gov/rtips/index.do). Vallance et al. [146] have translated a step-counter-based program into an iBook format (Fight Breast Cancer with Exercise), and Schmitz et al. [68] have translated a resistance training program to a publicly available DVD (Strength and Courage, exercises for breast cancer survivors). The BEAT Cancer implementation toolkit is anticipated to be ready for broader use by 2019. Other resources can be found outside the RTIPS website through cancer advocacy groups and by contacting study investigators.

Table 15.4 Possible solutions and safety considerations related to common cancer-related physical activity barriers

Barrier	Possible solutions and safety considerations
Fatigue	Energy conservation by setting priorities, periodization, and scheduling physical activity at times of peak energy
	Screen for anemia and avoid physical activity if severe
	Avoid overtraining
	Start slow and increase gradually
	Give physical activity time to reduce fatigue
Pain	Regulate physical activity based on tolerance; try intermittent bouts of 5–10 min
	Adapt the physical activity to minimize pain (e.g., non-weight-bearing activities)
	Advise cancer survivor to seek advice from health-care provider regarding pain management
Peripheral neuropathy; balance difficulties	Hold handrails if walking on a treadmill
	Avoid exercising on uneven surfaces
	Use physical activity to gain confidence and strength
Decreased range of motion due to surgery or radiation	Adapt exercise prescription to minimize discomfort
	Non-resistive range of motion exercises as appropriate
	Advise cancer survivor to ask their health-care provider about a physical therapy referral
Ostomy, stoma, hernia risk (e.g., colorectal cancer survivors)	Choose an exercise mode that allows loose fitting clothing
	Choose a private exercise location until confidence is gained in managing the ostomy during exercise
	Empty bag immediately prior to exercise bout
	Avoid exercise that causes excessive intra-abdominal pressure
	Avoid water and contact sports
	Wear an ostomy belt
	Wear abdominal support or truss during exercise that increases abdominal pressure
	Follow physician guidelines regarding exercise restrictions (and obtain physician clearance before initiating weight training)
	Follow established practices for infection management/prevention
	Consider supervision by trained exercise professional (especially for weight training)
Dry mouth and/or airway secretions (e.g., head and neck cancer survivors)	Keep a bottle of water close by while exercising
Fracture risk (osteoporosis, bone metastasis)	Limit fall risk and avoid extreme twisting
	Low impact workouts
Weakened immune system	Adjust exercise prescription based on tolerance
	Avoid public exercise facilities
	Avoid swimming
Lymphedema	Wear a compression garment if appropriate for location of lymphedema
	Exercise in a climate controlled or cool setting when wearing the compression garment
	Wear loose fitting clothing
Gastrointestinal side effects (e.g., nausea, vomiting, diarrhea)	If severe, avoid exercise and recommend cancer survivor seek treatment from a health-care provider
	If mild, intermittent 5–10 min bouts of exercise that can be done at home
Poor physical endurance with or without cardiac or pulmonary toxicity	Slow, gradual exercise progression
	Supervision by trained exercise professionals, if indicated
	Tailor the exercise progression to physical limitations

Table 15.5 Application of health behavior theory constructs to physical activity behavior change program strategies and elements

Theoretical construct	Strategies for targeting the construct	Program element examples
Perceived behavioral control and/or self-efficacy	Set feasible short-term exercise goals Self-monitoring Regularly review progress toward exercise goals	Self-monitoring device (e.g., step counter, fitness bracelet, exercise log) Attentive and positive reinforcement provided by staff and/or program tools Encourage practice and generalization of the exercise behavior (e.g., combine on-site exercise with exercising on their own)
Barriers interference	Use individualized, adaptable exercise prescriptions Motivational interviewing Cancer survivor education regarding troubleshooting barriers with ongoing counseling support Education regarding exercise safety	Access to program staff with expertise in dealing with exercise barriers faced by cancer survivors Cancer survivor education materials (e.g., print, web-based, etc.) Exercise sessions with trained exercise professional that allow safe individualization of the exercise prescription progression Provide a list of local exercise resources
Planning and/or goal setting	Set specific program and exercise goals Provide education regarding assessing prescribed exercise intensity	Education materials regarding setting a goal Goal setting worksheet Exercise prescription with ongoing review and update by program
Intention	Increase awareness of exercise benefits and safety early in the cancer survivor experience	Community and clinic-based outreach activities (e.g., information in newsletters, staff attendance at support groups, educational emails, integration with local oncology practices)
Subjective norm and/or social support	Educate and assist cancer survivors in identifying individuals who can facilitate meeting their exercise goals Facilitate group interaction around exercise	Group exercise Social media Telephone counseling with conference calls Engaging the health-care provider in reinforcing exercise

15.8 Recommendations

Given the benefits and safety of physical activity in cancer survivors, it is recommended that cancer survivors engage in at least 150 min per week of at least moderate intensity physical activity (Table 15.2) [33, 34]. Strength training 2–3 times a week is also recommended along with balance training, when appropriate. Stretching exercises after exercise are important for optimizing range of motion and limiting injury. Advice from trained exercise professionals may be required to safely tailor the exercise prescription based on an individual's physical limitations and cancer side effects [34]. Health-care providers can and should play a central role in encouraging and facilitating cancer survivors' physical activity [147, 148].

15.9 Progress over the Past Decade and Need to Transfer Evidence-Based Research to Survivorship Care

The scientific knowledge base from rigorous randomized controlled trials supporting the efficacy of exercise training in cancer survivors during and after treatment has markedly increased over the past decade [21–24]. Although studies initially arose from the nursing and kinesiology fields, broader awareness and interest among oncology providers have grown as the impact of physical activity on important clinical outcomes such as chemotherapy adherence [149, 150] and cancer recurrence/mortality has been reported [46]. Nevertheless, uptake of evidence-based

data into policy and routine, standard of care for cancer survivors has been slow [151], and few cancer survivors currently meet physical activity recommendations [6]. Further dissemination and implementation research is needed to better understand effective strategies and create sustainable infrastructure and policy that enhances the reach of evidence-based physical activity and exercise training interventions [151]. For example, to our knowledge, only one physical activity behavior change intervention for cancer survivors with reported efficacy has also been tested for effectiveness (an important step in the translational research continuum); this evidence-based telephone intervention remained effective when translated for implementation by peer coaches [116]. Hybrid effectiveness-implementation study designs combine effectiveness testing with assessment of implementation outcomes to speed the translational research process [152]. This approach was used to test an evidence-based resistance exercise training program for breast cancer survivors when translated to a community setting and implemented by non-research staff (effectiveness confirmed and factors important to the implementation process were identified [intervention fit within the local context, intervention adaptations, cost issues, etc.]) [153].

15.10 Future Directions

The field must move beyond "exercise is good" to understanding who (subgroups more likely to experience benefit or risk; personalized medicine), why (mechanisms; understudied outcomes), when (at what point during the cancer journey), what (optimal exercise dose for achieving the desired outcome), and how (enhancing physical activity and exercise adherence; dissemination and implementation). Future research is needed to determine exercise risks and benefits in cancer survivors with understudied cancer types and cachexia. Moreover, exercise effects on understudied outcomes (e.g., treatment adherence, cognitive function) also warrant attention. Identifying factors that influence an individual's response to exercise can be used to optimize exercise interventions using targeting or tailoring strategies. Furthermore, a precision medicine approach based on molecular and genetic tumor characteristics holds promise for better understanding the role of exercise as a potential adjunctive treatment for cancer [154].

Physical activity behavior change research is needed for understudied cancer types, increasing resistance training adherence, achieving longer-term maintenance of behavior change, and identifying intervention "active ingredients." Application and adaptation of health behavior theories should be emphasized as technology is increasingly integrated into behavior change interventions (application to increase intervention effects on behavior and adaptation because large sample sizes not previously available due to logistical barriers will allow theory testing and refinement). Moreover, participants agreeing to enroll in behavior change intervention trials are primarily cancer survivors who are already interested in increasing their physical activity, and as such, little is known about increasing intervention engagement by cancer survivors not typically self-selecting for trial participation. Hence, future research should focus on strategies effective in increasing exercise adoption.

Efficacious exercise training and physical activity behavior change interventions should be moved along the translational research continuum such that effectiveness (especially cost-effectiveness) is determined, as such data influence intervention acceptability and potential adoption by implementers and third party payers. Such research should be combined with assessment of implementation science outcomes influencing implementation success (e.g., hybrid effectiveness-implementation studies). Furthermore, improving sustainability of exercise and related behavior change programming (once implemented) is a critical yet understudied aspect [155]. Doing so requires identifying program characteristics and environmental factors predicting and influencing sustainability over time (e.g., intervention complexity, resource requirements, adaptability, and facilitation of institutionalization) [156].

15.11 Summary

In summary, exercise results in multiple biopsychosocial benefits in cancer survivors and may reduce risk of breast or colorectal cancer recurrence and mortality. Data consistently supports recommending regular physical activity after cancer diagnosis (150 weekly minutes of moderate-to-vigorous aerobic physical activity and resistance training 2–3 times weekly), and these recommendations have been integrated into clinical care guidelines [34, 157]. This coupled with the reduction in physical activity reported in cancer survivors emphasizes the importance of understanding and achieving physical activity behavior change in this population. Furthermore, the field of physical activity behavior change in cancer survivors has advanced dramatically over the past decade identifying important strategies for assisting cancer survivors in adopting more physically active lifestyles. Translating published research data to broader dissemination and implementation while continuing to address scientific knowledge gaps is critical to advancing the discipline of improved cancer survivor health and well-being through exercise training and physical activity.

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Nutrition and Weight Management

16

Virginia E. Uhley and Kai-Lin Catherine Jen

16.1 Introduction

The prevalence of obesity is a global epidemic [1]. It is estimated that in the United States, 68.8% 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, 2]. The major medical complications associated with obesity include metabolic syndrome, type 2 diabetes, cardiovascular disease, hypertension, and certain types of cancers [1, 3], to name a few. Cancer types strongly associated with obesity include kidney, esophagus, colon, gallbladder, pancreas, endometrial, ovary, and postmenopausal breast cancer [4, 5].

There are several potential mechanisms connecting obesity with the increased risk of cancer or recurrence:

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 [6, 7].
2. Hyperinsulinemia/insulin resistance. Hyperinsulinemia and insulin resistance are the cornerstones of metabolic syndrome and are commonly seen in obese individuals [8]. Hyperinsulinemia/insulin resistance reduces the production of insulin-like growth factor-binding protein-1 (IGFBP-1) and IGFBP-2 and 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 [9–11].

In addition, hyperinsulinemia is correlated with reduced production of sex hormone-binding globulin [12]. 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 [13, 14].

Other metabolic abnormalities observed in obesity as part of the metabolic syndrome include

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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 [15–17].

3. Other metabolic alterations. Obesity is characterized with elevated blood leptin levels [18, 19]. 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 [19]. Leptin has been reported to be angiogenic [20, 21] and has been postulated to be the link between obesity and prostate cancer [22, 23], breast cancer [24, 25], colon cancer [26], as well as cancer in other sites [27].

16.2 Body Weight and Cancer Recurrence

Obesity is not only a risk factor for cancer occurrence but also a risk factor for cancer recurrence [28, 29], poor prognosis for survival [30, 31], and increased risk of cancer mortality [32]. The increasing prevalence of obesity in the general population and the associated risk of various cancers will mean that many cancer patients will enter treatment overweight [33]. Weight gain after diagnosis can also adversely affect cancer prognosis and survival [31].

Weight gain is common in breast cancer patients, especially in those who are receiving adjuvant chemotherapy or are younger than 60 years of age [34, 35]. In a comprehensive review of observational studies on breast cancer recurrence or survival, Rock and Demark-Wahnefried reported that increased BMI and/or excessive adiposity was a significant risk factor for recurrent disease and/or decreased survival in a majority of the studies [29].

Concern with being overweight and weight gain are common issues among breast cancer survivors [29]. This weight gain after breast cancer diagnosis may be attributed to reduced physical activity [36] and altered dietary patterns [37]. 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 given the adverse consequences of weight gain after cancer diagnosis; continued efforts to identify the underlying mechanisms and develop appropriate weight management interventions to support long-term survivorship are of high importance [38, 39].

16.3 Dietary Intervention and Body Weight Changes in Cancer Survivors

Maintaining body weight within healthy ranges may help reduce risks of a variety of chronic diseases including cancer. 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 implemented to assist cancer survivors in losing weight. Dietary intervention trials aimed at increased intakes of fruit, vegetable, and fiber and reduced fat intake have usually been shown to be effective in achieving short-term goals and resulted in weight loss during the first 6 months of the intervention [40]. 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 [41]. Thus, even though the intake of fruit, vegetables, 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 [42]. 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 [43]. However, Blanchard et al. reported that 47% of the cancer survivors did improve their dietary quality [42, 44].

Cognitive behavioral weight management interventions that emphasize increased physical activity and diet modification have also been shown to promote significant weight loss and favorably alter body composition and blood lipid profiles among overweight and obese breast cancer survivors [45–47]. The current evidence supports the hypothesis that intentional weight loss can reduce cancer risk and that even modest levels of weight loss among the obese may be beneficial for cancer risk reduction [48]. However, better designed long-term studies on intentional weight loss are still needed to investigate the impact that weight loss has on survival for overweight and obese cancer survivors [49].

Overall, however, there has been very little clarity about the best nutrition practices for the prevention of cancer recurrence [50]. In 2012, the American Cancer Society issued a report summarizing the findings of a group of experts outlining the best clinical practices related to nutrition and physical activity for cancer survivors. The report provides three specific guidelines, including (1) the recommendation to attain and sustain a healthy weight, (2) the need to take part in regular physical activity, and (3) the recommendation to follow a dietary pattern with an increase in vegetables, fruits, and whole grains [51]. Other recommendations in this report provide reasonable conclusions to guide survivors with answers to common questions frequently asked as well as information relevant to selected cancer sites. In a systematic review, Hoedjes et al. provide an overview of the effectiveness of lifestyle interventions for overweight survivors of any cancer type after completion of initial treatment, and there is good support for this approach but concluded that there is lack of knowledge on long-term effectiveness [52] (see Table 16.1).

We have also employed different weight loss regimens to compare the effectiveness of weight loss and maintenance in breast cancer survivors [77, 78]. In one 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.
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, only the individualized and comprehensive groups had statistically significant weight loss as compared to their baseline weight (Table 16.1), and only the comprehensive group also reduced a significant amount of body fat. 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.

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 studies have been resource intensive [79]. In addition, dietary interventions may achieve the goal of increasing fruit and vegetable intake and reducing fat intake in breast cancer survivors. However, without energy restriction, weight loss is still not likely to be achieved [41] (Table 16.2).

Since weight loss can prevent cancer incidence and recurrence, as well as other chronic diseases [3], weight loss has been a goal for many obese individuals and cancer survivors for years.

Table 16.1 Overview of study characteristics of recent and ongoing studies of cancer survivors by cancer type that include weight loss/lifestyle change interventions[a]

Author (yr.)	Intervention type	Duration (follow-up)
Colorectal cancer		
Anderson (2010) [53]	PA + diet (LiveWell)	3 months
Colorectal, breast, and prostate cancer		
Morey (2009) [54]	PA + diet (RENEW)	12 months
Demark-Wahnefried (2012) [55]	PA + diet (RENEW)	12 months
Christy (2012) [56]	PA + diet (FRESH START)	10 months (1 and 2 years)
Postmenopausal breast cancer		
Befort (2012) [57]	PA + diet	6 months
Campbell (2012) [58]	PA + diet	24 weeks
Thompson (2015) [59]	Diet (CHOICE)	6 months
Thomson (2010) [60]	Diet	6 months
Breast cancer		
Demark-Wahnefried (2014) [61]	PA + diet (DAMES)	12 months
Djuric (2009) [62]	PA + diet (+spirituality)	18 months
Flynn (2010) [63]	Diet	2 × 8 weeks; 6 months
Greenlee (2013) [64]	PA + diet (curves program)	6 months
Harrigan (2015) [65]	PA + diet (LEAN)	6 months
Mefferd (2007) [45]	PA + diet	16 weeks
Patella (2009) [66]	Diet	12 months
Rock (2015) [46]	PA + diet (ENERGY)	24 months
Saquib (2009) [67]	Diet (WHEL)	4 years
Sheppard (2016) [68]	PA + diet (stepping stone)	12 weeks
Spark (2015) [69]	PA + diet	6 months
Stolley (2009) [70]	PA + diet (moving forward)	6 months
Swisher (2015) [71]	PA + diet (get fit for the fight)	12 weeks
Travier (2014) [72]	PA + diet	12 weeks
Vitolins (2014) [73]	PA + diet	12 weeks
Breast and endometrial cancer		
McCarroll (2015) [74]	PA + diet (lose it!)	1 month
Endometrial cancer		
Von Gruenigen (2008) [75]	PA + diet	6 months
Von Gruenigen (2012) [76]	PA + diet (SUCCEED)	6 months

PA physical activity
[a]Table adapted from Hoedjes et al. [52]

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 [80].

For many obese individuals, this weight loss/regain cycle repeats many times thus producing a weight yo-yo or weight cycling phenomena. In animal research we have previously reported that experiencing this kind of weight cycling showed insulin resistance [81]. Moreover, animals that went through five cycles of weight cycling had similar body weights as the control animals who maintained a constant body weight throughout the study [82]. 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 [83].

These animal data indicate the potential of weight cycling to promote breast cancer. However, we also observed that when insulin resistance was not produced, weight cycling did not increase the risk of breast cancer [84]. Therefore, it may be the insulin resistance perse,

Table 16.2 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 ± 1.9[bc] *	−9.5 ± 2.7[b] *	<0.005
BMI (kg/m^2)	0.5 ± 0.9[a]	−1.5 ± 1.0[ac]	−3.0 ± 1.3[bc] *	−3.7 ± 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[b *f*]	<0.05
Energy intake (kcal)	−145 ± 179	−570 ± 58 *f*	−515 ± 118*	−393 ± 163*	Ns
Dietary fat intake (%)	5.4 ± 3.7*	−2.6 ± 2.8*	−4.8 ± 1.5*	0.9 ± 3.4	Ns

Adopted from Jen et al. [77] 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

not the weight cycling itself, that increases cancer risks. Cleary et al. reported that weight cycling reduced the incidence of mammary tumors [85]. 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 [86].

16.4 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 (i.e., low fat/high carbohydrate, high protein/low carbohydrate). Significant improvements in weight and metabolic indexes can be demonstrated among overweight breast cancer survivors adherent to either a carbohydrate- or fat-restricted diet [59, 60, 87, 88–96].
2. Reducing food intake and eating a balanced diet, thus reducing energy intake (i.e., energy-restricted DASH, Mediterranean, MyPlate, or plant based) [57, 63, 97–100].

The American Society of Clinical Oncology (ASCO) has recently published position statements on obesity and cancer, nutrition, and physical activity guidelines for cancer survivors [33], as well as a guide with resources to encourage medical professionals to help patients lose weight and make other healthy lifestyle changes [101]. Demark-Wahnefried et al. recommend that medical professionals need to work together to provide support for healthy lifestyle changes in cancer survivors [102]. An individual's dietary preferences can strongly impact dietary adherence and weight-loss success and are an important consideration in the development of clinical practice guidelines for physicians who recommend that their patients lose weight [103–105].

16.5 Altering Dietary Composition

16.5.1 Low-Carbohydrate (CHO), High-Protein/High-Fat Diets

This type of diet has enjoyed widespread popularity. 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 [106–108]. In addition, elevated insulin levels inhibit the release of the brain satiety

hormone serotonin [109]. 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 [106–108].

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 [110, 111]. 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 [112]. Low-CHO diets also generate ketones because of incomplete fat catabolism [113]. 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 [114].

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 [115]. However, the long-term effects of a low-CHO/high-protein diet on hunger perception warrant further investigation. High-fat diets, on the other hand, have weak satiety value and thus may lead to overconsumption [116]. 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 [110, 111]. This improvement may be explained by the weight loss. Since individuals consuming low-CHO diets lost more weight at the beginning of the diet [60, 81], 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 [91, 109, 117]. 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 [118], foul taste in the mouth [119], weakness [120], constipation [120], headache, and dizziness [121]. Many of these symptoms are similar to those reported during and/or following radiation and various types of chemotherapy [122, 123]. Increased urinary calcium excretion may increase the risk of developing osteoporosis [124]. Treatment for breast and prostate cancer will also increase the risk of osteoporosis [125] suggesting that a high-protein/high-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 [126]. 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 [126].

These inconsistent results point to the need for further study to examine the relationship between high-protein/high-fat intake, osteoporosis, and cancer occurrence and recurrence. Before a definitive answer can be made, it would be a good practice not to consume a high-protein/high-fat diet because of its association with other chronic diseases.

High-protein/high-fat diets allow for unlimited quantities of meat, cheese, eggs, and other high-protein/high-fat foods while severely restricting fruit and vegetable intakes. Yang et al. [127] 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 [128]. Nagle et al. [129] 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/high-protein intake and cancer recurrence at this point, given the fact that cancer patients are more likely to develop other chronic diseases [130] that are associated with high-fat/high-protein intake, it seems advisable for the cancer survivors to avoid diets high in protein or fat. Under energy restriction, participants on a low-fat diet who had increased the percentage energy intake from protein showed the greatest reduction in weight and cholesterol and a triglyceride reduction equally large to that of participants on a high-fat diet.

16.5.2 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 [131, 132] and Ornish's diet [133, 134]. Barnard [135] 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 [135, 136]. 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. [137] 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. [138] 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 [139]. 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 [140, 141]. 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 [110]. 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 [141]. Nevertheless, the difference between the diets disappeared at the end of 1 year.

The major focus of this dietary approach is 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 diet is vegetarian, while Pritikin allows for a limited amount of low-fat animal protein daily, no more than 3.5 ounces/day) [142]. Foods high in fruits and vegetables are usually low in energy density [143].

The energy densities of foods have been shown to be associated with body weight and BMI [143, 144]. 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 [117, 138, 145–147]. Nevertheless, Raben et al. [148] and Prewitt et al. [149] 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. [150] 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 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 [151]. 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 [152]. 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 [153]. Although weight loss was not the goal of these programs, some weight loss in the intervention groups have been observed in some reports [154, 155] although not in others [41, 42].

Among survivors of early stage breast cancer, adoption of a diet that was very high in vegetables, fruit, and fiber and low in fat did not reduce additional breast cancer events or mortality during a 7.3-year follow-up period.

The FRESH START study accrued a large sample of cancer survivors [56]. The interventions targeted both prostate and breast cancer survivors, whereas most lifestyle intervention trials have targeted survivors of a single cancer type. The intervention arm showed a sustained reduction in total fat intake relative to baseline. These findings suggest that tailored intervention resulted in better long-term dietary outcomes than standard materials, although both fostered improved adherence to healthy dietary behaviors in cancer survivors. Barnard et al. [155] reported consistent evidence from clinical trials supporting that the prescription of vegetarian (including vegan) diets reduces mean body weight in study groups, suggesting that they may be helpful for prevention and management of weight-related conditions.

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 [132, 136, 156, 157]. 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. However, there was no difference between these diets in the levels of blood lipids nor in glycemic control and insulin sensitivity [158]. On the other hand, high-CHO diets have been reported to increase blood triglyceride levels [142, 143, 149].

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 [157]. Kasim-Karakas et al. observed that when individuals on a high-CHO diet ad libitum, they lost weight but maintained their normal blood triglyceride levels [147]. However, when individuals were put on an euenergetic high-CHO diet to maintain their body weight, their blood triglyceride levels elevated. Others have noticed similar findings. Schaefer et al. reported that effects of a high-CHO diet on blood lipid levels were related to the body weight change [159]. 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 [159]. 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

Table 16.3 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

thus are high in fiber), the diet's adverse effects on blood lipid levels may be alleviated [160, 161]. Many of the "low-fat" food products on the market, on the other hand, are high in simple CHO, as demonstrated in Table 16.3.

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 [48], 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 [137]. The exposure to high-CHO-containing foods can result in a marked restraining effect on the expression of appetite [162].

There are data to support that individuals who consume a low-fat, high-CHO diet are perhaps more successful at maintaining weight loss [163–165]. 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. [166] 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.

16.5.3 Balanced, Energy-Reduced Diets

Diets in this category are represented by the Dietary Approaches to Stop Hypertension (DASH) diet [167], the Mediterranean diet [100], the 2006 American Heart Association Diet and Lifestyle Recommendations [168], and the National Cholesterol Education Program (NCEP) Step I diet [169]. These diets are designed based on the 2005 Institute of Medicine (IOM) Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids [170].

Pérez-Escamilla et al. [171] conducted a systematic review which supports a relationship between energy density and body weight in adults, adolescents, and children. They concluded that consuming diets lower in energy density appears to be an effective strategy for managing body weight. Several studies have reported that total caloric content was more important than diet composition for weight loss [172, 173] 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. [91], 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 produce the weight loss.

Without reduction in energy intake, even diets with high fruits and vegetable content would not achieve weight loss [41, 42]. 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 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 [91]. Dietary recommendations for weight loss should be based on the "American College of Cardiology, the American Heart Association, and the Obesity Society published guidelines for managing overweight and obesity in adults" [172].

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 and dietary patterns of these guidelines are shown in Table 16.4. Another recommendation for a balanced, low-energy diet plan is included in the 2015–2020 Dietary Guidelines for Americans [100], the Mediterranean eating plan, and the DASH eating plan (Table 16.5). The DASH diet emphasizes fruits, vegetables, and low-fat dairy products. The effects of the DASH diet on weight management are being evaluated prospectively in the ENCORE study participants. The present findings suggest that the DASH diet, particularly when augmented by exercise and weight loss, can offer considerable benefit to patients with high blood pressure and reductions in biomarkers of disease risk [175].

The American Institute for Cancer Research and the World Cancer Research Fund also published the *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective* which again emphasizes choosing plant-based diet plans, consuming plenty of fruits and vegetables, and maintaining a healthy body weight, among other recommendations [176].

The Mediterranean diet plan may be a useful tool to reduce body weight, especially when the Mediterranean diet is energy-restricted, associated with physical activity, and more than 6 months in length [177]. The Mediterranean diet has been shown not to cause weight gain, which removes the objection to its relatively high fat content. These results may be useful for helping people to lose weight [178].

From the research evidence collected thus far, it is clear that in order to help prevent cancer occurrence/recurrence, maintaining a healthy body weight and consuming enough fresh fruits and vegetables are critical. The NCEP's Step I diet includes these in their dietary goals:

Table 16.4 The American College of Cardiology, the American Heart Association, and the Obesity Society Guidelines for Management of Overweight and Obesity in Adults, 2013 [174]

A diet from the European Association for the Study of Diabetes guidelines, which focuses on targeting food groups, rather than formal prescribed energy restriction, while still achieving an energy deficit. (descriptions of the diet can be found in the full panel report supplement)
A diet 1200–1500 kcal/day for women and 1500–1800 kcal/day for men or a 500–750 kcal/day energy deficit
Higher-protein diet (25% of total calories from protein, 30% of total calories from fat, and 45% of total calories from carbohydrate), with provision of foods that realize an energy deficit
Higher-protein Zone™-type diet (5 meals/d, each with 40% of total calories from carbohydrate, 30% of total calories from protein, and 30% of total calories from fat) without formal prescribed energy restriction but with a realized energy deficit
Lacto-ovo vegetarian-style diet with prescribed energy restriction
Low-calorie diet with prescribed energy restriction
Low-carbohydrate diet (initially <20 g/d carbohydrate) without formal prescribed energy restriction but with a realized energy deficit
Low-fat vegan-style diet (10% to 25% of total calories from fat) without formal prescribed energy restriction but with a realized energy deficit
Low-fat diet (20% of total calories from fat) without formal prescribed energy restriction but with a realized energy deficit
Low-glycemic-load diet, either with formal prescribed energy restriction or without formal prescribed energy restriction but with realized energy deficit
Lower-fat (≤30% fat), high-dairy (4 servings/d) diets with or without increased fiber and/or low-glycemic-index (low-glycemic-load) foods with prescribed energy restriction
Macronutrient-targeted diets (15% or 25% of total calories from protein; 20% or 40% of total calories from fat; 35%, 45%, 55%, or 65% of total calories from carbohydrate) with prescribed energy restriction
Mediterranean-style diet with prescribed energy restriction
Moderate-protein diet (12% of total calories from protein, 58% of total calories from carbohydrate, and 30% of total calories from fat) with provision of foods that realize an energy deficit
Provision of high-glycemic-load or low-glycemic-load meals with prescribed energy restriction
The AHA-style step 1 diet (prescribed energy restriction of 1500 to 1800 kcal/d, <30% of total calories from fat, <10% of total calories from saturated fat)

Table 16.5 The DASH diet recommendations, 2015 [100]

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, and 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 MyPlate servings and portion sizes for commonly consumed foods are presented in Table 16.6.
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 [179, 180]. Omega-3 (ω-3) fatty acids improve insulin sensitivity and thus may reduce cancer risk [181, 182]. 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 [183]. 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 [179, 182], 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, and flaxseeds.

Table 16.6 USDA's MyPlate and serving sizes (2011) [186]

Fruit: 2 cups/day, 1 cup of fruits counts as
1 cup raw or cooked fruit
1/2 cup dried fruit
1 cup 100% fruit juice
Vegetables: 2 1/2 cups, 1 cup of vegetables counts as
1 cup raw or cooked vegetables
2 cups leafy salad greens
1 cup 100% vegetable juice
Grains: 6 ounce equivalents, 1 ounce of grains counts as
1 slice bread
1 ounce ready-to-eat cereal
1/2 cup cooked rice, pasta, or cereal
Proteins: 5 1/2 ounce equivalents, 1 ounce of protein counts as
1 ounce lean meat, poultry, or seafood
1 egg
1 tbsp peanut butter
1/4 cup cooked beans or peas
1/2 ounce nuts or seeds
Dairy: 3 cups, 1 cup of dairy counts as
1 cup milk
1 cup yogurt
1 cup fortified soy beverage
1 1/2 ounces natural cheese or 2 ounces processed cheese

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 [100, 167, 175]. These complex carbohydrates contain not only adequate amounts of fibers but also micronutrients that have been shown to reduce cancer risk [182]. 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 micro-nutrients and are strongly recommended to reduce the risk of cancer occurrence and recurrence. For more detailed fruit and vegetable choices, please visit http://www.fruitsandveggiesmorematters.org/. If fresh fruits and vegetables are not readily available, frozen or canned varieties are suitable substitutes [184]. For some cancer survivors with compromised immune systems, consuming raw vegetables may not be advisable [185] 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 can follow the NCEP's Step I dietary pattern, the Mediterranean diet pattern, the DASH diet pattern, or a plant-based diet pattern combined with energy restriction to reduce energy intake and thus body weight. All of these dietary patterns include goals to include adequate amounts of fruits and vegetables in the diet, which provide the advantage of the phytochemicals and dietary fibers contained in these types of foods, which have been shown 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. It is important to remember that the only component of energy expenditure that individuals have control over is physical activity.

16.6 Future Directions

Improvements in understanding the role of obesity and weight management in cancer survivorship have been made over a decade since we authored the original chapter. Specifically, there have been significant improvements in the design of dietary intervention protocols including an increase in the number of randomized control trials [52]. Although, lifestyle interventions for cancer survivors have remained focused on testing fitness, diet, and behavioral approaches, it is important to note that there have been significant advances in our understanding of the impact that increases in dietary quality, reduction of dietary fat intake, increases in fruit and vegetable consumption, and dietary patterns have on weight management in cancer survivors.

Current evidence also suggests that weight management is key to controlling prevalent comorbid conditions in this patient population [52, 68, 69, 71–76]. Ongoing studies such as the DIANA-5 study [187] and the SUCCESS C study [188] that investigate the effect of lifestyle intervention on weight control and cancer outcomes/recurrence should provide greater insight into the best methods of weight loss and maintenance for cancer survivors.

Clearly, all healthcare professionals should continue to encourage weight management in cancer survivors as a means to improve overall health [55, 58, 189–191]. We found very few weight control interventions for cancer survivors that addressed the impact that racial or ethnic factors may have on outcomes [192]. Such interventions are needed and can help reduce the disparities currently seen in cancer mortality rates [70].

Future research should also focus on promising technology-delivered and home-based lifestyle programs for cancer survivors. Outcome-based evidence is just beginning to be reported with positive results, for some of these technologies that could provide cost-effective approaches for the delivery of nutrition and exercise interventions for weight maintenance [54, 55, 96, 193, 194]. Finally, there continues to be major gaps

Table 16.7 Future research needs related to cancer survivorship

Needs	Goals
To collect long-term data (≥ 12 months) from dietary intervention trials	To establish evidence-based nutrition guidelines for effective weight loss/maintenance and in preventing cancer occurrence/recurrence
To develop plans to disseminate nutrition knowledge about evidence-based guidelines	To continue to increase public and cancer survivor-specific awareness of the health benefits of nutrition and weight loss 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 nutrition and behavioral strategies to reduce the risk of cancer occurrence/recurrence

in knowledge regarding the long-term efficacy of nutrition interventions for weight management prevention of cancer recurrence and/or prolong cancer-free life. Further research is needed to support the development of evidence-based nutrition guidelines for cancer survivors. These ongoing and future research needs are summarized in Table 16.7.

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Smoking

17

Jamie S. Ostroff, Kristen E. Riley, and Lara K. Dhingra

17.1 Introduction

Cancer survivors are at increased risk for the development of second primary cancers, cancer recurrence, treatment late effects, and other chronic health conditions. Certain behavioral risk factors such as persistent smoking increase the likelihood of adverse health outcomes, and therefore treatment of tobacco dependence has emerged as a target for reducing morbidity and mortality in cancer survivors. Approximately 10–30% of cancer patients report current cigarette smoking at the time of cancer diagnosis [1]. Smoking is now recognized as causally linked to at least 13 cancers, including cancers of the lung, esophagus, larynx, mouth, throat, kidney, bladder, liver, pancreas, stomach, cervix, colon, and rectum, as well as acute myeloid leukemia [2]. According to the 2014 Surgeon General's Report on the Health Consequences of Smoking [2], persistent smoking following diagnosis is associated with cancer-specific and all-cause mortality, increased likelihood for second primary cancer, increased risk for disease recurrence, poor response to treatment, and treatment-related toxicity. In addition, cancer survivors who continue smoking are at risk for other tobacco-related chronic, life-threatening medical conditions, such as heart and respiratory disease, and poor quality of life [3].

Despite the apparent risks of persistent smoking, approximately 60% of patients who are current smokers at the time of diagnosis will continue smoking following their diagnosis [1]. Driven by this cumulative evidence of the harms of persistent smoking and the benefits of cessation in cancer patients, several leading oncology professional organizations have strongly endorsed tobacco use assessment and delivery of smoking cessation advice and treatment as essential for high-quality cancer care. The American Association for Cancer Research (AACR) has also prioritized the need for basic, clinical, and translational research to better understand and reduce the risks of persistent smoking on cancer outcomes [4]. In response, the National Comprehensive Cancer Network (NCCN) has developed evidence-based, clinical guidelines for tobacco use assessment and cessation treatment delivery in the context of cancer care [5] and recommends guideline adoption for all cancer patients and survivors [6].

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Notwithstanding this momentum, barriers to the implementation of tobacco use assessment and treatment strategies are many, and adoption of smoking cessation into real-world oncology practice settings has been slow and inconsistent [5, 7, 8]. Although recent surveys demonstrate that oncology providers agree that promoting tobacco cessation is an important part of cancer treatment planning [9, 10], most cancer care settings have not yet established tobacco cessation treatment as standard care [11].

Cancer survivorship provides extraordinary opportunities, as well as challenges to promoting smoking cessation. By personalizing the harms of smoking and focusing efforts on the restoration and maintenance of good health, cancer diagnosis can be a catalyst or "teachable moment" for smoking cessation among cancer survivors and their tobacco-dependent loved ones [12–14]. However, cancer also confers unique barriers to smoking behavior change that must be overcome in order to promote smoking cessation among cancer survivors.

In this chapter, we will (1) describe the current evidence supporting the importance of providing smoking services to cancer survivors and their families; (2) review prevalence rates of smoking and cessation in this population; (3) 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 across all healthcare settings and by all providers; and (5) highlight future research directions for promoting smoking cessation in cancer survivorship across the trajectory of care. This review will focus primarily on cancer patients following primary treatment for cancer, but will also encourage access to smoking cessation services for family members and other caregivers, recognizing the importance of partner smoking status and caregiver health on patient outcomes. Also, because of the dearth of literature regarding other forms of tobacco use in the context of cancer care (e.g., smokeless tobacco), this chapter will focus primarily on cigarette smoking cessation [15]. However, interested readers are referred to reviews on smokeless tobacco [16, 17] as well as a paper [18] and policy statement [19] on the use of electronic cigarettes in the context of cancer care. Additional research on these other forms of tobacco use in cancer survivors is needed.

17.2 Rationale for Promoting Smoking Cessation Among Cancer Survivors and Their Families

Persistent smoking is associated with poor clinical outcomes for cancer survivors, including poor quality of life, increased risk of secondary cancers and recurrence, as well as increased morbidity and mortality [20]. Considered a warning for synthesizing the effects of smoking, the most recent (2014) Surgeon General's Report (SGR) on the Health Consequences of Smoking concluded—for the first time since its inaugural publication in 1964—that there is now sufficient evidence for a causal relationship between continued smoking and adverse health outcomes for cancer patients and survivors [2]. The report highlights that cessation improves prognosis and further establishes that continued smoking is associated with an increased risk for mortality (all-cause and cancer-specific) and second primary cancers and is causally related to recurrence, poorer treatment response, and increased treatment-related toxicity [21–32]. Accordingly, the 2014 SGR summarizes new evidence supporting the conclusion that smoking is not only the leading cause of cancer but that quitting smoking improves cancer prognosis and important cancer-related outcomes for cancer survivors [2]. A growing literature clearly supports the benefits of quitting smoking following cancer diagnosis.

While most of these studies focus on patients diagnosed with tobacco-related cancers, there is also evidence supporting the specific health benefits of cessation across non-tobacco-related cancer types. Cancer care providers are encouraged to offer personalized quitting advice regarding the health benefits of cessation as outlined in the following section to enhance quitting motivation in cancer survivors.

17.2.1 Biological Mechanisms

There is a robust and growing literature on the biological mechanisms underlying exposure to cigarette smoking and cancer etiology and progression, including the effect of carcinogens (e.g., nitrosamines, benzopyrene) in cigarette smoke on tumor growth (e.g., accelerated growth, progression, metastases, and recurrence) [20] and the effect on comorbid smoking-related diseases (especially cardiopulmonary disease) on treatment complications and outcomes. For more on mechanisms of carcinogenesis, disease pathways, pathogenesis, and nonspecific effects of exposure to tobacco smoke, see Warren et al. and the 2014 Surgeon General's Report [2, 20].

17.2.2 Survival, Second Primary Cancers, and Treatment Complications

Smoking cessation is associated with an improved length of survival following diagnosis [2], while continued smoking is linked to the risk of second primary cancers and treatment-related complications. A meta-analysis [2] showed that the RRs for all-cause mortality among former smokers were intermediate between never smokers and current smokers, suggesting that smoking cessation prolongs survival compared to persistent smoking. In one study, smoking cessation significantly reduced the risk of death compared to persistent smoking [33], while a meta-analysis [27] concluded that persistent smoking increased the risk for all-cause mortality. There is a dose-response relationship such that greater cigarette smoking consumption is related to a higher risk of cancer-specific mortality.

To date, over 30 studies have found a robust relationship between smoking and second primary cancers and a decreased risk with cessation [2]. Continued smoking elevates the risk for second primary breast, lung, and Hodgkin lymphoma [2, 34, 35]. Further, continued smoking in Hodgkin lymphoma survivors increases the risk of lung second primary cancer [36]. Multiple studies have demonstrated that cancer patients who quit smoking lower their risk of developing another new cancer [27, 37]. Interestingly, there is a synergistic relationship between smoking and treatment radiation therapy, such that smokers who were treated with radiation therapy have a greater risk of second primary cancers compared to smokers not treated with radiation therapy. Thus, this population should be targeted for smoking cessation. Other evidence demonstrates that smoking cessation also decreases cancer recurrence [2], with 51 studies to date showing that cessation is associated with a lower risk of progression of a number of cancers. Further, smoking cessation was also related to the risk of subsequent primary cancer in a retrospective cohort study [38] and is known to lower the risk of other tobacco-related cancers, including uterine cervical, pancreatic, colon, and kidney cancers [39].

Active smoking worsens the deleterious physical effects of treatment toxicity. For instance, persistent smoking among head and neck cancer patients may be the most important factor increasing treatment-related complications from surgery and radiotherapy, while patients who quit have been found to experience lowers rates of oral mucositis and vocal hoarseness [40]. Similarly, continued smoking in cervical cancer patients elevates the risk of major treatment-related complications from pelvic radiation, particularly gastrointestinal problems [41]. Finally, the pharmacokinetic effects of nicotine in cigarettes alter the metabolism of medications (beta-blockers, bronchodilators, analgesics, benzodiazepines, and phenothiazines) decreasing their efficacy and/or resulting in potentially higher dosages of medication [42].

17.2.3 Quality of Life/Symptom Control

Smoking cessation in cancer survivors is associated with significant improvements in quality of life, including appetite, sleep quality, energy, and emotional well-being, while continued smoking is related to poorer quality of life [43]. In fact, lung cancer patients who smoke have the lowest

quality of life of any cancer patient, perhaps in part due to the smoking-related cancer stigma experienced and reported [44, 45]. Cancer patients and survivors who 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 [46].

17.3 Prevalence of Smoking and Cessation in Cancer Survivors

Despite awareness of the risks of continued smoking and the health benefits of cessation, the prevalence of smoking in cancer survivors is surprisingly high and somewhat similar to the general US adult population. Population-based estimates from the 1998–2001 National Health Interview Survey (NHIS) data show that 12% of cancer survivors are current smokers [47] compared to 16.8% of adults in the general US population [48]. Of even greater concern, Underwood and colleagues identified that 27% of cancer survivors diagnosed with tobacco-related cancers continue to smoke following diagnosis. Further, smoking rates in cancer survivors show significant age-specific, cancer-specific, and time since treatment trends [49]. Younger cancer survivors (18–44 years old) are more likely to report current smoking (33.3%) compared to their age-matched cohort with no history of cancer (20.9%). Notably, [47] 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 (≥10 years) (22.7%). Further, smoking rates are highest among gynecologic cancer survivors (37.3%) and survivors of lung and upper aerodigestive cancers combined (20.6%) with the highest rates of smoking reported in cervical (46.0%) and uterine cancer survivors (29.4%) [47]. Most prominent are findings showing that more than half of younger cervical cancer survivors (59.3%) report current smoking [50, 51]. Rates of smoking cessation have been reported in naturalistic and intervention studies with cancer survivors; however, there is much variability in quit rates across cancer types and treatment modalities [48, 52–59].

17.4 Clinical Practice Guidelines for the Delivery of Smoking Cessation Interventions

Clinical practice guidelines exist for the delivery of brief advice and evidence-based smoking cessation interventions in healthcare settings [60]. 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 [61]. More recently, an abridged model has been recommended: (1) ask, (2) advise, and (3) refer/connect [62]. In summary, the 5 As counseling model offers healthcare clinicians an evidence-based framework for promoting smoking cessation (Table 17.1).

Clinical practice guidelines for treating tobacco use and dependence, first published in 1996 and then updated in 2000, 2008, and 2016, are based on an expert panel's comprehensive and systematic review of the evidence base for the management of tobacco-dependent patients [5, 63]. The seven key clinical recommendations and findings are summarized in Table 17.2. 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 [61, 63]. The guidelines also highlight the efficacy of smoking cessation pharmacotherapies (i.e., bupropion, 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

Table 17.1 The "5 As" 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

Guidelines available from: https://bphc.hrsa.gov/buckets/treatingtobacco.pdf

Table 17.2 Clinical practice guidelines: findings and recommendations

Tobacco dependence is a chronic condition that often requires repeated assessment and intervention
Efficacious and cost-effective tobacco dependence treatments are available
Consistent identification, documentation, and treatment of every tobacco user in healthcare settings by all providers
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

Guidelines available from: https://www.iaslc.org/sites/default/files/wysiwyg-assets/nccn_smoking_0916.pdf

placebo [63]. Varenicline is also a first-line safe and effective cessation medication. Combination cessation pharmacotherapy has also been demonstrated [64] to be safe and effective. Minimal or brief counseling interventions for smoking cessation (e.g., lasting less than 3 min in duration) significantly increase tobacco abstinence rates, and higher-intensity interventions (e.g., lasting over 10 min) are nearly twice as effective as brief advice. Multicomponent cessation interventions in which healthcare 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 two-fold increase in quit rates [63].

17.4.1 Smoking Cessation Interventions in Cancer Care

Recognizing the prevalence and risks of continued smoking in cancer survivors, many professional oncology organizations, including the Oncology Nursing Society [65, 66], the American Society of Clinical Oncology [67], the American Association of Cancer Research [68], and the National Comprehensive Cancer Network [6], 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 [69, 70]. These recommendations include: 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.

Few randomized smoking cessation clinical trials with cancer patients have been published. A recent systematic review and meta-analysis did not find any significant treatment differences in quit rates among different approaches and concluded that the combination of both pharmacological and behavioral counseling approaches appears effective [71]. The review also highlights study limitations such as limited sample sizes, primary focus on lung and head and neck cancer patients, and lacked biochemical verification of self-reported smoking status. Although significant superiority of one treatment over another has not been demonstrated, 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 well-established smoking cessation interventions [72–74]. More recently, Park and

colleagues are testing a more intensive tobacco treatment intervention for cancer patients [75]. There is a need to examine the best practices for promoting smoking cessation among cancer survivors. Several cancer centers are developing innovative strategies to integrate smoking cessation services into cancer care settings [76, 77].

17.5 Challenges of Promoting Smoking Cessation in Cancer Survivorship

There are many challenges in delivering smoking cessation interventions to meet the special needs of cancer survivors, and the solutions must focus on the contextual factors that mediate and moderate smoking cessation outcomes [78–81]. Most studies have focused on the treatment- and smoking-related characteristics of lung and head and neck cancer patients [82].

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 as discussed below (Table 17.3).

Table 17.3 Smoking cessation in cancer survivor

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

17.5.1 Patient-Related Barriers to Smoking Cessation

There are numerous patient-level barriers to smoking cessation for cancer survivors, including high nicotine dependency, perceived urgency of cessation advice, cancer-specific health beliefs, psychological distress, disease- and treatment-related factors, stigma, social network influences, and misreporting of smoking status. Patients diagnosed with tobacco-related cancers typically report long histories of heavy tobacco use [80]. Heavy cumulative tobacco exposure is associated with strong nicotine dependency and severe withdrawal symptoms (e.g., cravings, restlessness, difficulty concentrating, and insomnia) following smoking abstinence.

The perceived urgency for abrupt and immediate cessation following cancer diagnosis may also compromise quitting self-efficacy and thereby the likelihood for long-term smoking abstinence. Smoking cessation programs typically 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 is understandably disrupted. In addition, patients' pre-quit planning and problem-solving skills may be overwhelmed by psychological distress related to cancer diagnosis. Anecdotally, we have found that smokers who are able to quit with use of counseling and cessation medication prior to hospital admission are more likely to maintain long-term smoking abstinence into extended survivorship. Patients, even those who express strong motivation to quit, should be supported to develop competencies in coping with smoking urges and counseled regarding the risk of smoking lapse and relapse.

Cancer patients may report low response efficacy or a lack of knowledge about the specific health benefits of smoking cessation in relation to cancer outcomes. Indeed, tobacco-dependent cancer patients often report fatalistic health beliefs such as "the damage is done" and that "it is too late to quit" [83]. Cancer survivors' lack of

knowledge about specific health risks of smoking (e.g., impact on cancer recurrence or second primary cancer) may be a potent obstacle to smoking behavior change [84]. Wold and colleagues [84] 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 [84]. To address these health belief barriers, healthcare providers should offer personalized advice about the short- and long-term benefits of smoking cessation when addressing patients' concerns about cancer risk factors, medical late effects, and preventing disease recurrence. 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. Counseling support and targeted behavioral 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 [85–87].

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 [88]. Heightened psychological distress has been reported along the entire continuum of cancer care [89, 90]. 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 [88]. Cancer survivors with high levels of negative affect or, in particular, those survivors with comorbid anxiety or depressive symptoms may be at acute risk for continued smoking or relapse. Indeed, by exacerbating illness and cancer worry, persistent smoking itself is a stressor. Unlike many of the uncontrollable aspects of cancer and its treatment, smoking cessation affords patients the opportunity to be active participants in their cancer treatment and recovery. Intensive cessation treatment for patients and survivors with high-risk profiles for relapse (e.g., greater nicotine dependency, past or current depression, low quitting self-efficacy) must be evaluated to determine whether they are superior to brief treatments.

Disease- and treatment-related factors 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 patients indicate that smoking relapse is highest within the first month following hospital discharge [91, 92]. As cancer 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, 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 [49, 78]. 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 innovative approaches that address these problems in cancer survivors is needed [93, 94].

Other lifestyle factors related to cancer are related to increased likelihood of smoking and decreased likelihood of quitting as well. Those survivors with more modifiable health-related factors such as smoking, physical activity, and

high BMI were less likely to seek out healthcare, where smoking cessation services are more readily available [95, 96]. Regular assessments of health-related factors should be incorporated into survivorship care plans to reduce smoking and increase smoking cessation.

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 [97]. 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. Secondhand smoke exposure is shown to be high in community-dwelling cancer survivors in the United States, according to national data from 1999 to 2012 [98]. Among patients with head and neck cancers, the presence of other household smokers, most commonly a patient's spouse, is a significant predictor of smoking resumption [74]. Including family members in follow-up visits and taking time to encourage them to seek assistance for quitting is often necessary and can provide an opportunity for caregivers to further support their loved ones. Survivors of childhood cancers have also been shown to be at increased risk of smoking [99]. Specifically, peer smoking, smokers in the household, binge drinking, suicidal behavior, and no history of CRT were all related to the patient-level risk factors for smoking in this large group.

Cancer survivors may be reluctant to disclose their smoking status to healthcare providers or family members [74], a factor impeding tobacco treatment referral and engagement due to fears of strong disapproval and criticism. Misreporting of nonsmoking ranges from 15% to 33% and is typically higher among recent former smokers [100–102]. The usage of a standardized tobacco use assessment [70] which serially assesses patterns of smoking reduction before, during, and after cancer diagnosis may enhance the accuracy of disclosure of current smoking status by survivors.

17.5.2 Provider-Related Barriers to Smoking Cessation

Lack of training has been identified as needed for promoting smoking cessation in cancer care [103]. It is also important to raise awareness about the risks of persistent smoking and the benefits of cessation for cancer survivors among primary healthcare providers as the majority of cancer survivors will receive follow-up care in primary care settings. Innovative strategies for tobacco treatment must enhance the competency and capacity of both generalists and specialists who provide posttreatment care and expand training in best practices for tobacco dependence to other disciplines. Inadequate staff training and pessimistic provider attitudes may impede the delivery of smoking cessation interventions. Surveys report many primary healthcare 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 [104, 105]. Findings estimate that smoking status is assessed in 50%–66% of clinic visits [106].

Within the cancer care setting, Sarna and colleagues [107] surveyed members of the Oncology Nursing Society (ONS) to assess cessation practice patterns as well as 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 were lack of patient motivation, 74%; lack of staff time, 52%; lack of cessation counseling skills, 53%; lack of knowledge about how to help patients quit, 40%; not wanting to add to patient's stress, 35%; not wanting patients to feel guilty, 24%; and a lack of perceived benefit due to patients' poor prognosis, 23% [107]. Assessing attitudes and enhancing competency toward the delivery of smoking cessation interventions are important

areas for provider training [107]. Further, provider education to dispel myths and misconceptions about smoking cessation in cancer care is key. For instance, oncology nurses identified lack of patient motivation as a deterrent to providing cessation counseling [107], yet national surveys indicate 70% of current smokers actually want to quit smoking [48]. Oncology [108] patients report similarly high rates of quitting motivation.

17.5.3 System-Related 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 [109]. Although reimbursement for smoking cessation interventions has improved, there are limitations to the coverage of tobacco dependence treatment, particularly intensive treatment. Although mandated as an essential health benefit, less than 33% of employers provide full coverage for smoking cessation interventions [110]. These services often require expensive co-payments, limited coverage for face-to-face counseling (instead favoring less costly web-based or printed materials for self-help programs), referral guidelines, and public health programs that may not meet the specific needs of cancer survivors. However, there have been advances in recent reimbursement trends [111]. Further, between 1997 and 2002, the percentage of healthcare plans that provide full benefits for pharmacotherapy tripled. Tobacco dependence treatment is currently covered under Medicare Part B (2005), i.e., two cessation attempts annually and a maximum of four intermediate sessions (3–10 min) or intensive sessions (>10 min) 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. The passage of the Affordable Care Act also improved cessation treatment coverage; however, efforts at short-term cost reduction may erode some of these essential health benefits.

Relatedly, the lack of universal screening for patients' smoking status represents another important systems-based gap and barrier to smoking cessation service delivery. The National Cancer Institute has led an effort to develop and disseminate standardized assessment of tobacco use in cancer clinical trials [112]. It is recommended that clinicians (both in oncology and primary care) providing follow-up care to cancer survivors assess smoking status in the context of cancer diagnosis, active treatment, and posttreatment. Widespread adoption of a standardized tobacco assessment 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 would allow 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] (Table 17.4).

17.6 Clinical Care Approaches for Promoting Smoking Cessation in Cancer Survivorship

A variety of approaches and models have guided the delivery of smoking interventions in cancer care settings [76, 114, 115]. Tobacco interventions have involved stepped-care strategies, treatment-matching strategies, and tailored intervention strategies. Tobacco treatment delivery approaches range from minimal contact, self-help interventions to intensive counseling interventions delivered by certified tobacco treatment specialists. All cessation support approaches should include recommendations for use of FDA-approved cessation medications that have been found to be safe and effective for use by nicotine-dependent cancer survivors [93]. Combination uses of nicotine replacement therapies are well-tolerated.

Table 17.4 Barriers to addressing tobacco use among cancer patients/survivors

Patient barriers
Psychological distress
Stigma
Low quitting self-efficacy
Heavy nicotine addiction/withdrawal symptoms
Lack of knowledge and concerns about safety and effectiveness of cessation medications
Misreporting of current smoking behavior
Other smokers in household
Provider barriers
Competing priorities
Lack of time
Perceived patient resistance
Discomfort discussing smoking with patients
Lack of knowledge about nicotine addiction and tobacco dependence treatment
Lack of confidence in how to help patients quit
Systems barriers
Lack of standardized tobacco use assessment
Lack of integration within electronic health record
Lack of tobacco treatment champion
Lack of cessation resources and referral options
Lack of clarity regarding roles and responsibilities
Lack of clinical workflow
Lack of reimbursement

Our smoking cessation program at Memorial Sloan-Kettering Cancer Center follows a stepped-care model (see Fig. 17.1), with all frontline cancer care providers trained and expected to provide "Step 1," advice and minimum intensity counseling (effective referral to our embedded Tobacco Treatment Program) to patients. "Step 2" includes moderate-intensity counseling through referral to the smoking cessation program, in which certified tobacco treatment specialists (TTSs) (oncology 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 clinical psychologists who provide specialized care of smokers at high risk (i.e., comorbid psychiatric or substance abuse condition) for continued smoking in individual counseling sessions. Our program recognizes and fully integrates the unique psychosocial needs of tobacco-dependent cancer survivors (e.g., psychological distress, treatment side effects, and functional disability).

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. Serial assessment of current tobacco use and treatment of tobacco dependence should be required elements of the survivorship dare plans. Delivery of evidence-based tobacco treatment (behavioral counseling and cessation pharmacotherapy) should be integrated into the comprehensive care of survivors being followed in primary care and community oncology clinics. 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 are critical. Evidence-based self-help cessation guides, online cessation support provided by the National Tobacco Quitline (1–800–784-8669; www.smokefree.gov) and the American Society of Clinical Oncology (https://www.asco.org/), are available to providers to support their efforts. 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. For tobacco-dependent survivors with high 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 beneficial. The dissemination of best practices for long-term follow-up in cancer survivors will include the tailoring of cessation interventions for this growing population.

[1]These patient education materials are available from the authors by request.

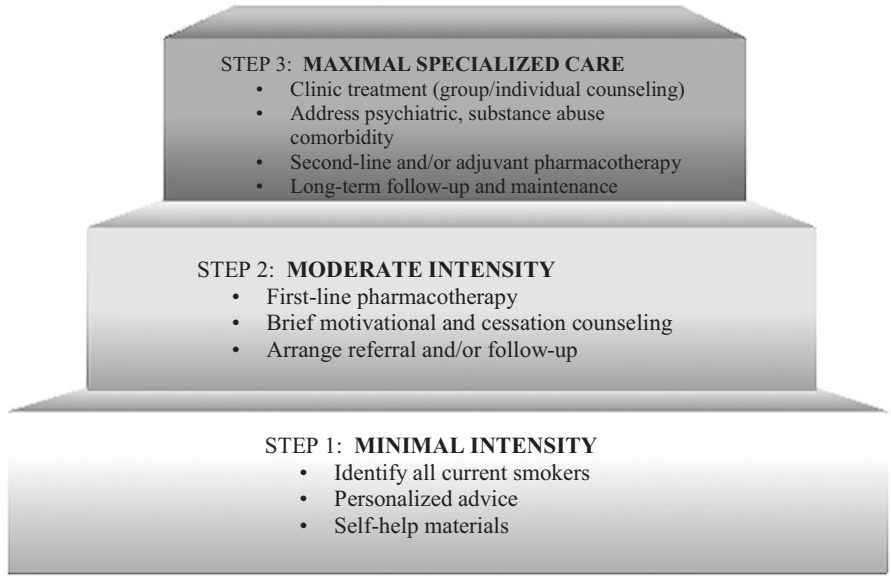

Fig. 17.1 Memorial Sloan-Kettering Cancer Center Smoking Cessation Program Stepped-Care Model

17.7 Future Directions

Recognizing the relatively high rates of smoking among patients and the persistent risk for smoking resumption in survivorship, there is a need to develop, evaluate, and embed 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. Dissemination and implementation research and approaches is important in developing a sustainable smoking cessation intervention.

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 are likely to be relevant to the cancer survivor population [77]. For instance, Schnoll and colleagues [116], recognizing the potential barrier of psychological distress, conducted a randomized clinical trial examining whether combination pharmacotherapy including bupropion (in addition to NRT and counseling) increases quit rates in head and neck cancer patients over and above NRT and behavioral counseling alone. 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.

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. 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. Future knowledge about nicotine metabolism and precision pharmacotherapy recommend may advance targeted cessation pharmacotherapy interventions for cancer survivors.

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 [5]. For patients and survivors who are recent quitters, some have recommended

consideration of biochemical verification (e.g., alveolar carbon monoxide ratings). Referral for more intensive cessation treatment within the broader context of psychosocial support services that consider 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.

Another consideration includes smoking-related stigma and decreased disclosure and treatment seeking. Recent research by Ostroff and colleagues [117] have shown that lung cancer patients in particular report stigma about their illness, as they and others perceive lung cancer as having occurred due to ones' own choices (i.e., smoking cigarettes). There are currently ongoing efforts to develop effective and empathic communication strategies to assess and treat tobacco dependence among cancer patients. Use of other tobacco products such as e-cigarettes should be further studied within the cancer survivor population. In particular, there is much interest and controversy in the role of electronic cigarettes as cessation aids.

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 tested the effectiveness of disseminating a multicomponent behavioral and pharmacological cessation treatment using a web-based delivery model [118]. These findings 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.

In 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. Cancer diagnosis has been widely described as a "teachable moment," for smoking cessation in that the diagnosis increases perceptions of personal risk and related expectations of positive or negative outcomes, prompts a strong emotional response, and redefines self-concept or social role [12, 69, 119]. Given dramatic rates of observed cessation among cancer survivors, evidence suggests that the context of this teachable moment facilitates smoking behavior change 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 follow clinical guidelines for embedding smoking cessation services into cancer care. Further research is needed to address the unique patient, provider, and systems-level challenges to the delivery, uptake, and long-term effectiveness of smoking cessation interventions for the growing cancer survivor population.

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Part VI

Health Care

Primary Care

18

Baukje Miedema

18.1 The Story of a Cancer Patient

In early October 2003, a 52-year-old university professor, with two teenage sons, presented to a family physician (FP) in a "walk-in clinic," because his own FP was unable to see him for the next 4 weeks. He had a hard lump on the right side of his throat. He was prescribed antibiotics. The lump continued to grow rapidly in size. Two weeks later, he went again to the "walk-in clinic" as his FP was unavailable on short notice. He was referred to an ear, nose, and throat (ENT) specialist. After delays due to inconclusive results and additional consultations, he was ultimately diagnosed with diffuse large B-cell non-Hodgkin lymphoma (DLBCL). He was treated with cyclophosphamide, vincristine, doxorubicin, and prednisone, followed by a course of radiation. During this time, he only saw his FP once, to discuss the diagnosis. Following treatment, he was judged to be in complete remission and left acute cancer care in late April 2004:

> For his cancer follow-up care he saw the medical and radiation oncologists at 3-month intervals. He underwent serial imaging for the next 4 years. Five years after treatment was completed the patient had routine primary care related visits to the FP, none focused on cancer.
>
> Over a decade later, the patient noticed a small lump on the left side of his neck. Because of his previous experience, there was an immediate suspicion of a recurrence of DLBCL. The patient called his new FP's office - the previous FP had retired - and a CT scan was ordered. He was referred to an ENT and several biopsies were taken. Ten days later the FP informed the patient that the DLBCL might have recurred. He underwent additional biopsies and second opinions, until the diagnosis of a new primary was made. During the patient's second active treatment, which included chemotherapy without radiation, he did not see the FP.
>
> About 4–5 months post second cancer treatment; the patient was admitted to hospital with an ischemic thrombotic stroke. He was found to have severe stenosis of his right carotid artery, a late effect of his initial radiation therapy. He underwent stenting of his carotid artery, and then returned to the care of his FP. He was also prescribed antiplatelet medication and a statin to help prevent future strokes.
>
> Over the summer the patient saw the FP once, complaining that his recovery seemed slow. By the end of August, the patient felt intolerably tired and weak. He made an appointment with the FP and heart function (given prior cardio toxic chemotherapy) and blood tests were ordered. His haemoglobin (HB) levels had dropped, possibly related to a gastrointestinal bleed secondary to blood thinners. Over the following six months, patient has regained stable health status and sees the FP as needed every three months which will soon turn into six months, and then annually if he remains stable.

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18.2 Cancer Care: It is Complicated!

This is a sanitized description of the experiences of an actual patient. This story provides only some of the clinical side of his case and does not discuss the emotional, psychological, financial, and physical impact of the cancer diagnosis on his survivorship phase and on the patient's family. While the story has a "good ending" because the patient survived all the major health issues, his cancer is currently in remission, and he has recovered fully from the stroke. However, there were gaps in his care, and he has suffered late effects including a second malignancy and carotid stenosis, the treatment of which potentially led to his bleeding. The significance of this story for this chapter is the patient's weaving in and out of the primary and tertiary health-care systems over years beginning with the original presentation and diagnosis, being "lost" during treatment but finding a home again following treatment, resurfacing and being lost again with the second cancer, and then clearly falling into primary care following cancer-related complications.

Although every cancer patient's story is unique, there are many similarities with other cancer patients' experiences regardless of the type of cancer. Overall, health care for cancer patients is complex; many health-care workers, representing various disciplines such as primary and tertiary medicine, nursing, complementary, and alternative, and social and psychological services, may be involved during the cancer trajectory of the patient. In fact the American Cancer Society (ACS) has listed more than 60 health and allied health-care providers as being professionals that may be involved in cancer care for a given patient [1]. In addition to the medical complexities, various social variables such as social-economic status, ethnicity, age, geography, and gender may create additional challenges for cancer patients during all stages of the cancer trajectory [2–6].

Patients in certain rural areas may have access to small regional hospitals; however, Australia and Canada, and in remote areas in the USA, have populations who live in areas which are often isolated and difficult to reach. Some remote areas are only "fly-in" communities. Many cancer diagnostics (i.e., scans) and treatment options require highly trained staff and need to be operated for many hours to make them cost-effective; hence, they are usually only accessible in larger urban centers and not in small rural or remote areas impacting rural cancer care severely [7]. These disparities also present severe challenges for delivery of care after cancer treatment. To add to the complexities of cancer care and particularly cancer follow-up care, there is great variability in care [8].

Over the last two to three decades, there has been a push toward a shift in the location of where cancer follow-up care is provided [8, 9]. All cancer care, including cancer follow-up care, was traditionally the domain of the tertiary or hospital system, and primary health care was rarely involved in cancer care except for the consult of the presenting symptoms. Until the 1990s it was not uncommon that the majority of family physicians felt that specialists should provide cancer care, including cancer follow-up care, and belonged in the hospital setting [10]. Over the years, the number of cancer patients has significantly increased for a number of reasons, resulting in the tertiary health-care system being overwhelmed by the number of cases [11]. For example, in Canada alone between 1986 and 2015, the number of cancer cases, both for women and men, has almost doubled [12]. The number of cancer survivors has also increased due to better diagnostic and treatment options and lower mortality [11]. As a result, more and more cancer follow-up care is moved out of the tertiary health-care system into primary health care. Thus PHCPs see more patients that have survived cancer [13]. This is particularly true for countries in the Western world with robust health-care systems.

However, due to the large number of health-care providers potentially involved in the care of a cancer patient, after the completion of the intensive (adjuvant) treatment, it is not always clear to both the patient and the clinicians who are in charge of the patient's cancer follow-up care: the specialist or the PHCP? [14] Patients like to have clarity about who to turn to and often feel a bit lost during the transition from active cancer treatment to cancer follow-up care [15].

In this chapter, the author examines the rationale, challenges, and workable models of primary health care as an integral part of cancer survivorship in selected countries. This chapter will include a description of a few models of primary health care in countries such as Canada, the USA, some European countries, Australia, and New Zealand to provide the context for cancer survivorship care in the primary health-care system. Further, a new development in oncology services, often in rural areas, is the development of "community oncology," or oncology care provided by primary health-care providers.

18.3 Primary Health Care in Select Nations

The importance of primary health care was enshrined in the Declaration of Alma-Ata in 1978 [16], but the majority of global citizens, as of today, still do not have access to PHCPs. Primary health-care provides a safe and cheaper model of care that improves the health of the entire population; unfortunately, globally, this Declaration of Alma-Ata "remains mostly unfulfilled" [17, 18]. In general, when referring to PHCPs, the focus is on family physicians or general practitioners; however, in many countries nurse practitioners (NPs) also are considered PHCPs. In Canada and the USA, NPs can have independent primary health-care practices, while in the Netherlands, they work under the immediate supervision of a general practitioner [19–21].

Countries with robust primary health-care systems have the best population health outcomes on several indicators demonstrated decades ago [18, 22]. Nevertheless, mostly due to the increasing cost of health care, many countries, with a universal primary health-care system, allow market forces to creep in to control cost [23]. The Netherlands, which had a universal health-care insurance with a robust primary health-care system, changed their universal health-care insurance to a "private insurance for all" in 2006 [24]. At this time there is no indication that the new scheme is better than the old [24]. New Zealand launched a new primary health-care strategy in 2001 to improve the population's health. New Zealand has a mixture of public and private health insurance, and almost all its citizens have access to a PHCP [25]. The primary health-care system in the USA is not robust; its health-care system is the most expensive in the world, but still has poor outcomes compared to other countries [26]. The Affordable Care Act (ACA) expanded the health insurance coverage for citizens who could otherwise not afford to buy health insurance, and hence access to (primary) health care was improved [27]. Finally, Canada's overall health-care system is the individual responsibility of each of the ten provinces and three territories. Each province has a single payer system in which all necessary medical services are covered [28]. The challenges with the Canadian health-care system are the wait-times for necessary procedures and a shortage of PHCPs in many parts of the country [28].

Despite the promise of the Declaration of Alma-Ata, even in the countries with very well-functioning health-care systems including excellent primary health care, many are struggling with access, wait-times, and cost. To illustrate this, the Commonwealth Fund report of 2015 measured access across many countries. Just to highlight a few findings, New Zealand is achieving better same-day access than Canada, while the US performance is between Canada and New Zealand [29, 30]. Accessing diagnostic tests was least problematic in the Netherlands and most problematic in New Zealand. Canadian doctors have to wait the longest (more than 15 days) to get information on their patient after hospital discharge [29].

18.4 Community Oncology

In addition to primary health care provided by PHCPs, several countries have developed what is called "community oncology." How the latter is defined and how it is applied vary greatly from country to country. Oncology services such as the administration of chemotherapy are traditionally associated with large tertiary cancer care institutions or hospitals in bigger centers. The eastern Canadian province of New Brunswick with a population of 750,000

people has three major hospitals with medical oncologists providing chemotherapy. Therefore, some small hospitals far from oncology units rely on general practitioner oncologists (GPOs) to administer chemotherapy as prescribed by the medical oncologist. This is referred to as "community oncology." Thus in Canada "community oncology" is defined as cancer therapy, including chemotherapy, delivered in small hospitals outside the larger tertiary cancer centers [31]. In Canada over 50% of patients receive chemotherapy in community oncology clinics [31].

General practitioner oncologists (GPOs) are family physicians with a specific focus and often additional training in oncology [32]. Some work in hospital settings, others outside the hospital settings. Many work both in the hospital and in primary health care in the community [32]. The tendency in Canada is to use more and more community oncology clinics, while in the USA, the tendency is to move away from "community oncology" [31, 33]. It is important to distinguish this model of "community oncology" from that in the USA where this is defined as medical oncologists (specialists) who work in private practice (group or solo) and are not part of a hospital or academic or teaching institution [34]. In Canada, GPOs bridge the gap between large tertiary cancer centers and smaller communities. A similar model is being proposed in the USA whereby an "oncogeneralist" would bridge the gap between hospital-based oncology and primary care with a focus on survivorship care [35, 36]. Despite the potential advantages of this model, there are concerns such as safety in chemotherapy administration, long-term feasibility, and lack of interest on the part of the primary care physicians, among others [36].

18.5 Primary Health Care and Cancer Follow-Up Care

18.5.1 The Rationale

A landmark randomized control trial indicated that routine cancer follow-up care for breast cancer patients was equally well carried out by PHCPs as by cancer specialists [37]. Before this robust RCT, the assumption was that specialists would detect recurrence more easily. A more recent study indicated that women with breast cancer who also received care during the follow-up phase from their PHCP receive better preventive and mental health care as well as care for other comorbid conditions than patients who only receive follow-up care from a cancer specialist [38, 39]. A systematic review of the literature concluded that both PHCPs and patients are in favor of more primary health-care involvement during adjuvant treatment as well as during cancer follow-up care [40].

Continuity of care and having one main health-care provider during cancer follow-up care are very important to patients [41, 42]. Continuity of care leads to better health outcomes, and during the cancer follow-up care phase, a patient is much more than just their cancer. They may have a multitude of other health issues, related to their cancer treatment or not, hence the importance of continuity of care. According to the *American Academy of Family Physicians* (AAFP), continuity of care is the primary objective of primary health care and "… Is concerned with quality of care over time. It is the process by which the patient and his/her physician-led care team are cooperatively involved in ongoing health care management toward the shared goal of high quality, cost-effective medical care" [43].

Intentionally, or unintentionally, patients also see the importance of continuity of care because they do consult the PHCPs regularly during cancer follow-up care as is demonstrated by two recent studies. A large Canadian study, the *Canadian Team to Improve Community-Based Cancer Care along the Continuum* (CanIMPACT), examined various aspects of the cancer trajectory for breast and colorectal cancer patients in Canada, with a focus on the interaction between cancer specialists and PHCPs. In one sub-study, the role of breast cancer specialists in cancer follow-up care, using administrative data from four Canadian provinces representing roughly one third of the population, was examined [44]. The most frequently visited physician in the 4 years

of follow-up care, starting at 1-year post diagnosis, was the PHCP.

Almost all breast cancer patients who were in follow-up care made visits to both the cancer specialist and the PHCP [44]. Although there was significant variation among the four provinces, the highest number of visits to the PHCP in year 1 post diagnosis was an average of 7 visits, and by year 4, it had dropped to an average of 5. The majority of these visits were not cancer related. Also disease stage had no impact on the number of visits. As would be expected, patients with comorbid conditions had more frequent PHCP visits. Over the 4 years of data collection, breast cancer-related visits to the PHCP declined steadily, as did visits to the cancer specialist [44]. Thus this Canadian study has demonstrated that during cancer follow-up care, the PHCP sees the cancer patient very regularly, although the authors do indicate that "oncologists continue to deliver most of the cancer related follow-up care…" [44]. This is also consistent with other studies in the USA and the Netherlands [45–47].

18.5.2 Palliative Care

Although the focus of this book is on cancer survivors, which usually focuses on the time after acute cancer treatment has been completed; patients do not always survive their cancer. Based on the Canadian Cancer Society statistics, 1 in 4 patients will not survive their cancer, which will be the cause of their mortality, and in the USA, more than 500,000 people will die of cancer annually [11, 12]. Therefore, a brief discussion of palliative care is justified in this chapter. Often, when adjuvant treatment is futile, many cancer patients move into palliative care with a focus on the relief of suffering and improvement of quality of life [48]. The majority of palliative care patients are those with cancer [49].

Many palliative care physicians have roots in family medicine or general practice. Some have additional training, whereas for others it is part of the continuity of care for their patients. Palliative care can be provided in many different settings; the most common settings are acute hospitals, hospice centers, long-term care facilities, and private homes [50]. Nevertheless, a Canadian study concluded that just over half of patients die at a location of choice [51]. Home visits from PHCPs are an important factor for patients who received palliative care at home [51]. In a Scottish study, when patients were asked where they would prefer to die, patients familiar with hospice preferred the hospice and patients unfamiliar with hospice preferred to die at home. Few patients indicated that they preferred to die in a hospital; but unfortunately, there is a severe shortage of hospices in many countries [52, 53]. In some countries it is possible to die at home with hospice services. A 2016 study examined the utilization of palliative care among seven countries for cancer patients 65 and older. The USA (22.2%) and the Netherlands (29.4%) provided the least amount of "hospital centric" palliative care. In Belgium, Canada, England, Germany, and Norway, around half of the patients died in a hospital setting [54]. The cost of the last 180 days of care was highest in Canada followed by the USA and was the lowest in England.

A Canadian longitudinal study examining lung cancer patients argued that the PHCPs were not much involved with their patients during treatment, but when the cancer progressed, they became more and more involved and were the main health-care providers during the palliative phase of the disease [55]. However, in some cases the PHCPs feel ill prepared to deliver palliative care in the community [48, 56]. A survey by the *Canadian Hospice Palliative Care Association* of PHCPs indicated that most participants believe that palliative care is important, but half were comfortable providing palliative care outside the hospital setting [57]. An Australian study examined the perceptions of palliative care services focusing on caregivers. Overall the caregivers had a high satisfaction level with the palliative care services, but many felt that community-based palliative care services were inferior compared to care in an inpatient setting [58]. A study in the USA compared in-home/hospice palliative care to usual care. Patient satisfaction was greater with the home/hospice care than the usual care, and these patients had a reduced need for emergency room visits in the last stages of life, thus less costly care [59].

Part of palliative care treatment options is now medical assistance in dying (MAiD). The majority of patients who request assistance in dying are cancer patients in palliative care [60–63]. In some Western countries, MAiD has been possible since 1940. Canada, six American states, and six European countries allow MAiD. The requests for MAiD vary greatly from country to country; 20% of PHCPs in the USA have received a MAiD request, while in Belgium and the Netherlands, this number is around 60%. In most countries it is the primary care physician who provides the assistance in the dying process for the patient. Thus, MAiD has become an extension of palliative care [60–63].

18.5.3 Cancer Follow-Up Care

Sometimes patients can be very conflicted about having to transition all their cancer follow-up care to the PHCP despite the fact that they want their PHCP involved in their cancer care, preferably during the entire cancer care trajectory [64–66]. In a Canadian study, many cancer patients, when transitioned to a PHCP after adjuvant treatment, expressed a feeling of being abandoned [67]. Their feelings are captured by the word cloud below [68] (Fig. 18.1).

In many cases, cancer patients may develop a strong attachment to oncology specialists [69]. Although cancer patients have extensive contact with their PHCP, and they may be very satisfied with the PHCP care during the cancer trajectory and during cancer follow-up care, they have reservations regarding their PHCP's knowledge about cancer-specific issues compared to the specialists [55, 70, 71]. In a US study, patients felt that oncology specialists are more knowledgeable than the PHCPs and therefore may be more able to detect a cancer recurrence [64].

Other challenges are that many patients are confused which clinician is in charge of their cancer follow-up care due to the lack of a clear transition of care plan [72–74]. A cancer specialist may still follow the patient for cancer-related issues after active treatment, but they do not treat other comorbid conditions nor do they deal with disease prevention strategies (cancer screening for other cancers) [73]. To compound the hesitation toward PHCPs handling cancer follow-up care, many patients do not even have access to a personal PHCP. In many countries, there is a shortage of PHCPs, although this may vary from region to region. Canada, Australia, and the USA report shortages of PHCPs, and in many cases, there is an uneven distribution between urban and rural areas, resulting in many patients not having access to a PHCP [75–77].

Not only are patients confused as to who is "in charge" of their cancer follow-up care, clinicians can also be confused [78]. There are several reasons for the uncertainty regarding of "who is in charge?" First, the role of the PHCP is often poorly defined; second, not all PHCPS are interested in providing cancer follow-up care [79, 80]. In a Canadian study, 24% of PHCPs were willing to take immediately and exclusive care of their prostate cancer patients, 22% for their colorectal cancer patients, 21% for their breast cancer patients, and 16% for their lymphoma patients. Over time this number increased to between 89% and 100% of their cancer patients; however, 11% said that they did not feel comfortable, under any circumstances, to look after their colorectal cancer patients [80].

Fig. 18.1 Word cloud of patient comments when transitioned to primary health care

Sometimes specialists are reluctant to relinquish their cancer care for their patients. In the UK, cancer specialists believe they are in the best position to provide clinical care during cancer follow-up care; hence 85% still followed their cancer patients after they had completed active cancer treatment even though they agreed that PHCP follow-up care would free their time for active cancer treatments [81].

A recent CanIMPACT study described the challenges with the "coordination of cancer care" between PHCPs and specialists [14]. Almost 60 specialists and PHCPs were interviewed for this qualitative study. The overall conclusion of the study is that proper communication between the various cancer specialists and the PHCPs is often lacking [14]. The enhancement of technical communication devices does not translate into better communication for a variety of reasons. One simple technology-related barrier was the incompatibility between software programs among departments, hospital, or other institutions. Sometimes the lack of rapport between the specialist and the PHCP is a hindrance to proper communication, but the biggest challenge for a smooth transition of active cancer care to cancer follow-up care was due to the unclear role division between the various types of clinicians [14]. Another CanIMPACT team looked at 24 models of care between the tertiary and the primary health-care system with 11 models focusing on cancer follow-up care [82]. Most models of care were based on breast and colorectal cancer. The review of these models of cancer follow-up care also referred to the incompatibility of electronic health records between the various clinicians. The most successful models of care and the best communication were often facilitated through a nurse navigator; however, most models of care lacked formal evaluation, and therefore at this time, it is unclear how well they work [82]. All these challenges and issues with the transition of cancer patients from active cancer treatment to cancer follow-up care and to the PHCPs' care are unfortunately not new. These problems have been identified for some time, if not decades [8, 9], and potential solutions need more aggressive policy and implementation efforts.

In summary, it is evident that PHCPs are very suitable to take on a significant role of cancer follow-up care for their patients. PHCP care is cost-effective, but above all it provides a seamless continuity of care for cancer patients for all their health-care needs. Still, patients, specialists, and PHCPs struggle with reservations to have their patients transitioned to PHCP care. The following section describes some existing and emerging models of cancer follow-up care that may enhance the transition of cancer follow-up care to PHCPs and enhance satisfaction of care for all involved.

18.6 Models of Cancer Follow-Up Care in Primary Health Care

The American Society of Clinical Oncology (ASCO) has listed a number of models of cancer follow-up care that range from oncology specialist care to a "community generalist model." For each model, there are several advantages and disadvantages. Even though we see more and more cancer survivors who require both, cancer and non-cancer follow-up care, the debate of how best to transition cancer patients to PHCPs after adjuvant treatment is still ongoing and evolving.

Patients and many clinicians believe that shared care models are most beneficial [83, 84]. ASCO argues that any optimal model depends on the "patients' needs, risk, and resources," with significant involvement of nurses [85, 86]. A Canadian study evaluated breast cancer transition models by regional cancer centers for Cancer Care Ontario [87]. Regional cancer centers (RCC) developed and implemented breast cancer transition models.

Three main models for cancer follow-up care were identified: (1) patients were directly transitioned to PHCPs; (2) the development of transition clinics with NP, GPO, and PHCPs; and (3) shared care models. In the shared care models, the patient received direct follow-up care from the PHCP, but with links to the oncology specialist [87]. Regardless of the model, all RCC used survivorship care plans (SCP). However, one critical component of these models of care with

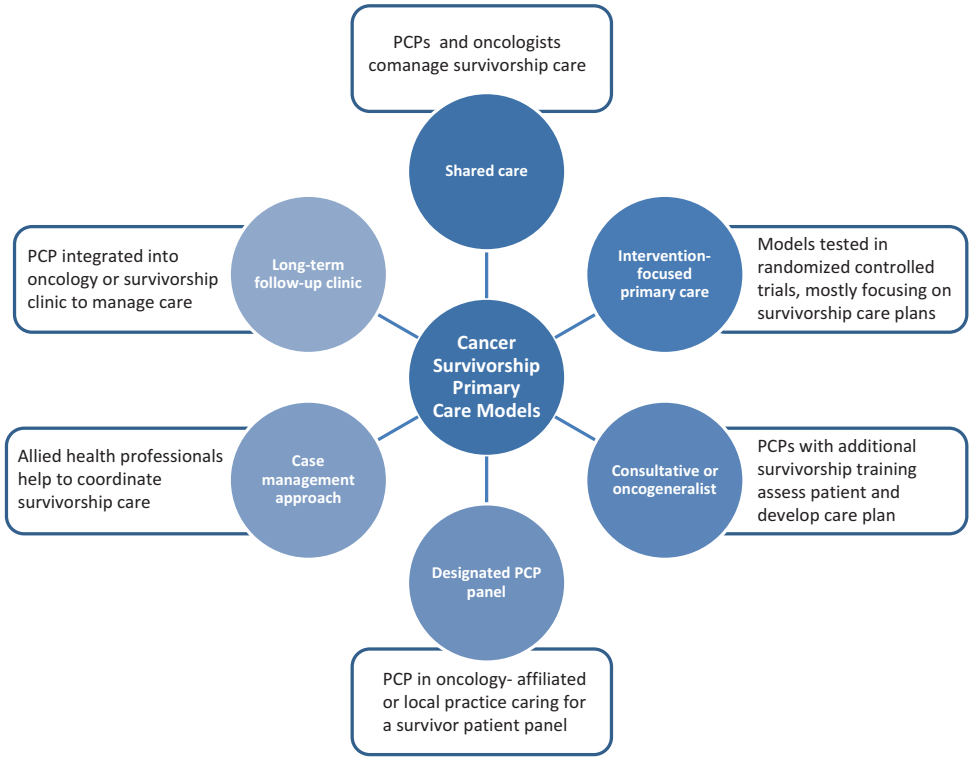

Fig. 18.2 Models of cancer care based on a scoping review [35]. (Reprinted from Nekhlyudov et al. [35])

various degrees of PHCP involvement depending on the local health-care structure and resources was the absolute necessity of adequate funding [87]. Brouwers et al. described several models of primary health-care involvement with cancer follow-up care across Canada [82]. The majority of the cancer follow-up care models use nurse navigators, and in a few cases multidisciplinary teams were created around the patient [82]. Nekhlyudov et al. published a scoping review of primary health-care involvement with cancer follow-up [35] (Fig. 18.2).

Other models that use PHCPs for survivorship care rely on multidisciplinary teams with a key person such as an oncology nurse navigators (ONNs) [82]. ONNs are highly trained nurses with oncology-specific knowledge [88]. ONN programs are not new. In the USA the first ONN program was initiated in the Harlem Hospital Center in New York City in 1990. Its original focus was on increasing the low screening rates in underserved populations. The American College of Surgeons Commission on Cancer has stated that by 2015, all accredited cancer institutes need to create a process to facilitate ONN staff [88]. Currently ONN programs encompass the entire cancer trajectory, including survivorship. The need of ONN is increasing, in part due to the shortage of PHCPs and cancer specialists [89]. Although the ONN models of care make a lot of sense, but as of today, there is still a lack of robust evidence for this model of cancer follow-up care, as well as the other models discussed [35, 82, 90–94].

Currently, the most urgent need seems to be that whatever cancer follow-up care model is used, processes need to be developed to measure efficacy and determine best practices regarding development and implementation and health outcomes. It goes without saying that for these evaluations, patients need to be involved and no "one size fits all" [95].

18.7 Future Directions

As summarized in this chapter, there are opportunities for PHCPs to be closely involved, if not lead, cancer survivorship care. There are a number of strategies including education and training, better clinical practice guidelines that include evidence-based recommendations. In addition, enhanced communication strategies need to be developed and for some countries (USA) financial incentives to provide care for a complex population of patients [35]. With respect to education, medical schools are particularly excellent places to start training physicians to create a "foundational framework for cancer survivorship" [35]. The same suggestion has been made for the enhancement of palliative care in primary health care [96].

As described earlier, training GPOs or oncogeneralist with expertise in oncology may have beneficial outcomes. GPOs are used more and more in Canada and bridge the gap between oncology and primary health care in various types of cancer settings [32]. Several provinces in Canada offer training programs for family physicians to enhance their oncology knowledge, and in many cases, they work closely with medical oncologists [97]. Although the training of GPOs is not consistent across the board, they work with a broad number of cancer patients [32].

As described earlier, information transfer and communication between oncology and PHCPs is suboptimal. As a way to enhance both, many have advocated for survivorship care plans (SCP) [79, 98, 99]. SCPs may also aid with the risk stratification of who should transition to primary health care based on the type and stage of cancer and comorbid conditions and who should remain in the tertiary care system [35]. SCPs enhance communication between PHCPs, cancer specialists, and the patients and make the follow-up care more predictable because the various care steps are clearly laid out [73]. Many cancer agencies in the USA, Canada, the UK, and other countries make models of SCPs available. There is not a uniform SCP because cancer follow-up varies greatly from cancer to cancer and because there is a huge variability of the health-care systems. Unfortunately, few studies have rigorously evaluated the efficacy of SCPs [100]. In addition to the poor evaluation of the SCPs, uptake in the clinical setting in the USA is also limited; only half of the cancer centers in the USA use SCPs [100, 101].

In summary, there are many arguments to be made for enhancing primary health care throughout the cancer trajectory. This seems specifically the case for cancer follow-up care, the longest phase of the cancer trajectory. PHCPs are uniquely positioned for this due to the discipline's holistic approach and its ability to treat patients with many different health conditions simultaneously. There are a number of studies that indicate that cancer patients can safely be transitioned to primary health care during the survivorship years, but there still is a lack of robust randomized clinical trials to indicate best practices. Most research has been carried out in small settings with small populations and mostly focused on the four most common cancers: breast, lung, prostate, and colorectal. Other cancers also need to be included in studies of how these patients can best transition to primary health care. To add to the complexity, primary health care varies greatly from country to country and inside countries. Cancer patients deserve a clear plan for the transition from acute cancer care to survivorship, because if cancer treatment is successful, in all likelihood the survivorship years will be longest and in need of the best quality, coordinated care that leads to the best quality of life possible.

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Comprehensive Healthcare

19

Erin E. Hahn, Jennifer Jones, and Karen L. Syrjala

19.1 Introduction

With advances in detection and progressively more complex treatments, two-thirds of people in the USA who are diagnosed with an invasive cancer will become long-term survivors [1, 2]. While the growing number of cancer survivors is a remarkable achievement, it is also challenging our current health systems within a climate of increasing constraints [3]. New models of care are needed along with programs to meet the needs of different types of cancer survivors. Understandably, cancer care systems and comprehensive cancer centers have historically been organized and funded to deliver acute care with the primary focus on cure and reducing mortality rather than promoting physical and psychosocial health [4]. Follow-up care has typically been provided by the primary treating oncologist and focused heavily on surveillance for recurrence. This model is neither adequate nor sustainable given the predicted growth in cancer survivors over the next decade and their broad survivorship needs [5–8]. For many, cancer can now be viewed as a chronic and complex disease. This "survivorship" framework requires a shift from a primarily acute, disease-focused approach to a wellness-centered, chronic care approach that moves beyond surveillance for recurrence and second cancers to also include detection and treatment of the late and long-term effects of cancer and its treatment. Health promotion is central in this new model to minimize dysfunction and/or disability and maximize well-being and overall quality of life [9–11].

Cancer survivors have unique post-treatment needs including risk of cancer recurrence and subsequent malignancies, persistent and late treatment effects, functional loss, and disability. They face multiple adaptive physical, functional, and psychosocial challenges as they transition back to their post-treatment lives [12–17]. While the evidence suggests that the majority of cancer survivors adjust well over the long term [18–21], a number of unmet needs of cancer survivors have been identified, and very few cancer survivors receive any comprehensive post-treatment survivorship care [9, 11]. Not surprisingly, patients commonly report they don't know what to expect once treatment is over. Some feel that they are not being cared for or describe feeling

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"abandoned" [22–25]. Consequently, over the last two decades, patient advocacy groups, expert consensus panels, and governmental reports have recommended improvement in the quality of post-treatment survivorship care to ensure continuity of care and to address the unmet needs of cancer survivors. In particular, these experts identify the need for support as cancer survivors transition from acute cancer treatment to the follow-up and/or palliative phase of the cancer trajectory [9] [26–29]. These efforts have resulted in broad agreement on the essential elements of survivorship care delivery, which include (1) prevention and detection of new cancers and recurrent cancer; (2) surveillance for cancer spread, recurrence, or second cancers; (3) interventions for consequences of cancer and its treatment (e.g., management of long-term and late effects); and (4) coordination between specialists and primary care to ensure ongoing and preventive care needs are met (e.g., immunizations, management of other chronic conditions). In addition, there is agreement on the importance of encouraging healthy lifestyle choices (i.e., tobacco cessation, exercise, healthy diet), assisting survivors in accessing community support services, and developing a detailed treatment summary and survivorship care plan [9, 30] to promote more effective communication and care coordination. Other suggested areas of need include patient navigation, transition care appointments, family and caregiver support, patient education and resources for ongoing needs, palliative care, and rehabilitation for long-term and late effects [31].

19.2 Milestones in Defining Models of Cancer Survivorship Care

19.2.1 Policy Documents

Post-treatment cancer patients are a heterogeneous population with unique healthcare needs related to their disease and treatment. As described in the seminal 2005 Institute of Medicine (IOM) report, *From Cancer Patient to Cancer Survivor: Lost in Transition*, transitioning from active treatment (e.g., surgery, chemotherapy, radiation) to ongoing post-treatment care, ongoing palliation, and/or ongoing maintenance therapy is a critical and distinct phase of the cancer care journey [9]. Recognition of cancer survivorship as a distinct phase of the cancer care continuum is often attributed to the 1986 article *Seasons of Survival: Reflections of a Physician with Cancer*, by Fitzhugh Mullan, MD, in which the author describes three phases of survival: acute, extended, and permanent [32]. Dr. Mullen concludes with a recommendation for a strategy to address ongoing survivorship needs. Since then, numerous milestones have further established survivorship as a fully accepted component of cancer care (Table 19.1). The National Coalition for Cancer Survivorship (NCCS) was founded shortly thereafter [33, 34], with Dr. Mullen as a co-founder; the Office of Cancer Survivorship was established at the National Cancer Institute in 1996, and in 2004 the Centers for Disease Control and Prevention partnered with the Livestrong Foundation to publish a National Action Plan for public health solutions to cancer survivorship issues [35]. The following decade (2005–2014) saw the development of the Survivorship Centers of Excellence Network [36], the publication of the Children's Oncology Group Long-Term Follow-Up Guidelines [37] and the essential elements of survivorship care [30], and the establishment of cancer survivorship committee within the American Society of Clinical Oncology [33]. Dedicated survivorship publications emerged, including the *Journal of Cancer Survivorship* [38], the first edition of the *Handbook of Cancer Survivorship* [39], and *Health Services for Cancer Survivors* [40]. A watershed point was reached with the mandate for treatment summaries and survivorship care plans for all cancer survivors by the cancer center accrediting arm of the American College of Surgeons Commission on Cancer (CoC) in 2012 [41]. By 2015, numerous models of cancer survivorship care were being proposed, developed, and tested [42].

However, with the progress, there have been recognized barriers. For example, as identified by

Table 19.1 Milestones in cancer survivorship care

Milestone	Date	Purpose/relevance
Seasons of survival: Reflections of a physician with cancer, by Fitzhugh Mullan, MD, *The New England Journal of Medicine*	1985 (published)	"The challenge in overcoming cancer is not only to find therapies that will prevent or arrest the disease quickly, but also to map the middle ground of survivorship and minimize its medical and social hazards"
National Coalition for Cancer Survivorship (NCCS)	1986 (established)	Founded by and for cancer survivors, NCCS' mission is to advocate for quality cancer care for all people touched by cancer
Office of Cancer Survivorship, National Cancer Institute	1996 (established)	The Office of Cancer Survivorship was created in recognition of the growing number of cancer survivors and the need for more research to better understand and meet their unique needs
Centers for Disease Control and Prevention's National Action Plan for Cancer Survivorship: Advancing Public Health Solutions	2004 (published)	This National Action Plan was created to help identify and prioritize cancer survivorship needs that will advance cancer survivorship public health efforts
Children's Oncology Group clinical practice guidelines for long-term care	2004 (first published and online clinical guideline)	This first published guideline for survivorship care has been updated regularly. Adult survivor guidelines have followed from various organizations (see Table 19.2)
From Cancer Patient to Cancer Survivor: Lost in Transition, National Academies Press	2005 (published)	A committee established at the Institute of Medicine of the National Academies examined the range of medical and psychosocial issues faced by cancer survivors and made recommendations to improve their healthcare and quality of life
Survivorship Centers of Excellence Network	2005 (initiated)	The Livestrong Foundation funded the Survivorship Center of Excellence Network, consisting of seven National Cancer Institute-designated comprehensive cancer centers, to accelerate the pace of progress in addressing the needs of the growing survivor community
Journal of Cancer Survivorship	2007 (established)	A dedicated survivorship journal publishing original research, systematic and meta-analytic literature reviews, clinical investigations, and policy-related research that can impact the quality of care and quality of life of adult cancer survivors
Handbook of Cancer Survivorship	2007 (published)	The first edition of a practical guide to meeting and managing the challenges of life after cancer and what clinicians, researchers, and health systems can do to ease the transition
Essential Elements of Survivorship Care Meeting	2011 (occurred)	The overarching goal of this multidisciplinary meeting of cancer survivorship stakeholders was to achieve consensus in the survivorship community around how to best address the needs of post-treatment survivors
American Society of Clinical Oncology (ASCO) cancer survivorship committee	2011 (established)	This committee ensures that the research, clinical care, and educational needs related to cancer survivorship are championed in all the activities of ASCO
Health Services for Cancer Survivors	2011 (published)	A comprehensive, integrative, evidence-based framework for improving the health of survivors over the long term and across clinical settings and specific diagnoses
American College of Surgeons Commission on cancer mandate	2012 (published for compliance by 2016)	For cancer centers to maintain their accreditation, this mandate requires compliance with the provision of a treatment summary and survivorship care plan to all cancer survivors without metastatic disease
Models of cancer survivorship care, Agency for Healthcare Research and Quality	2014 (published)	This in-depth report describes existing and proposed models of survivorship care for survivors with adult-onset cancer who have completed active treatment

the 2005 IOM report, short- and long-term physical and psychosocial healthcare needs of post-treatment cancer patients were not consistently recognized or addressed in clinical settings, large research gaps limited evidence on which to base models of care, and few cancer programs included specialized post-treatment care services. Several barriers to integrated survivorship care contributed to this problem, including the diversity of cancer types and treatments and the complex and siloed nature of cancer care delivery, which includes multiple specialists and multifaceted therapies [3, 43]. While ongoing research efforts particularly in the past decade have identified physical and psychosocial long-term and late effects in adult cancer survivors, there was little evidence or guidance on appropriate care and management of this growing patient population and limited, if any, models of survivorship care to draw on when designing the first dedicated programs for survivorship care.

The IOM report based on a consensus of providers, researchers, and advocates, in addition to other early efforts to increase awareness of post-treatment care (e.g., the National Coalition for Cancer Survivorship, the Livestrong Foundation), contributed to the development and growth of dedicated survivorship care programs [42]. Initially, survivorship programs relied in part upon the IOM expert consensus recommendations on components of post-treatment care to develop survivorship care programs, in addition to local clinical champions and expertise [36]. The IOM report reinforced the four essential components of survivorship care, as described above, and helped to lay the groundwork for emerging survivorship programs at academic and community care organizations. Other reports such as *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs* (2008) also outlined the importance of screening and treatment for behavioral and social needs in cancer patients and survivors [44]. However, survivorship programs in cancer centers needed a detailed guidance on the clinical management of adult cancer survivors, as well as tested models for delivering care, in order to establish effective programs that proactively address the ongoing health needs of this growing patient population.

19.3 Survivorship Guideline Development

Clinical practice guidelines are a resource for improving quality of healthcare delivery. They can be used to assist in designing and implementing standardized programs to efficiently deliver consensus and/or evidence-based care [45]. High-quality evidence-based guidelines provide objective information to shape the overall direction of care and inform development of quality metrics and methods of measurement. These guidelines can help to ensure that care delivery is safe, efficient, and equitable and may also reduce over- and undertreatment. Overtreatment and aggressive surveillance strategies are particular areas of concern in cancer survivorship care, where the prevailing ethos was traditionally "more is better" [46]. Likewise, underdiagnosis and undertreatment of non-oncology needs such as cardiometabolic monitoring, fatigue, insomnia, neuropathic pain, and other types of pain can be improved through broad dissemination of guidelines to both oncology and primary care providers [47].

Until recently, there was little evidence-based clinical guidance for adult post-treatment cancer care. Pediatric oncology has a long history of collaborative care, including the development and use of standardized treatment protocols and clinical guidelines. For example, as described in Table 19.1, in 2004 the Children's Oncology Group developed the Long-Term Follow-Up (LTFU) Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, which is a comprehensive, treatment exposure-based guideline [37]. The LTFU guidelines are wide-ranging and include social, physical, and behavioral long-term and late effects. The LTFU guidelines incorporate available evidence and expert opinion and are updated periodically with recommendations from collaborative, multidisciplinary workgroups. This treatment exposure-based approach to survivorship care is used to

coordinate much of pediatric survivorship care [48], including screenings, counseling, and other health services based on the surgical interventions, chemotherapy treatment (type, dose), and/or radiation dose and field received by the patient. There are many long-standing pediatric long-term follow-up programs, such as the programs at St. Jude Children's Research Hospital and at Children's Hospital of Philadelphia, both founded in the 1980s [49, 50].

Adult cancer survivorship care lagged behind pediatric oncology in both guideline and program development. However, efforts started in the late 1990s to develop and disseminate clinical practice guidelines for post-treatment adult cancer care. The American Society of Clinical Oncology (ASCO) developed a guideline for the surveillance and management of early-stage breast cancer in 1997, based on over 20 years of surveillance evidence including evidence from randomized trials of more- or less-aggressive post-treatment cancer surveillance in asymptomatic patients [51, 53]. The ASCO guideline committee recommended a less-aggressive surveillance strategy, which included physician visits and annual mammograms; they concluded that the evidence did not support use of advanced imaging modalities (e.g., computed tomography (CT) scans, positron emission tomography (PET) scans) or cancer antigen laboratory tests. The ASCO breast cancer surveillance guidelines were followed by a Cochrane systematic review that confirmed a lack of evidence for intensive surveillance for recurrence in this setting [53]. The ASCO recommendations have been reviewed and updated several times over the ensuing years, with little change to the primary recommendations [54]. In fact, the ASCO breast cancer surveillance recommendations are now a part of the ASCO "top 5" list in the American Board of Internal Medicine *Choosing Wisely* campaign, which is focused on limiting the use of low-value healthcare services [46].

Other disease-specific guidelines for the care of adult cancer survivors soon followed, responding to the need for evidence synthesis and clinical guidance (Table 19.2). ASCO and other organizations, including the American Cancer Society (ACS), the National Comprehensive Cancer Network (NCCN), and Cancer Care Ontario (CCO), developed and disseminated surveillance guidelines for prostate, colorectal, and breast cancer, among others [54–57]. The process for guideline development is summarized in the ACS guideline for prostate cancer survivorship care [55]. The recent ASCO/ACS breast cancer survivorship guideline was jointly developed [58], while in some instances, guidelines are endorsed (e.g., head and neck cancer survivorship [59]). Other survivorship guidelines have been developed to address specific cancer- and treatment-related symptoms and long-term and late effects that may arise in post-treatment adult cancer care, regardless of cancer type. For example, these guidelines focus on the prevention and management of chemotherapy-induced peripheral neuropathy [60], and screening, assessment, and management of fatigue [61] may be applicable to a wide variety of cancer types. Recommendations for post-treatment psychosocial care also exist; a recent Pan-Canadian guideline for the screening, assessment, and management of psychosocial distress, depression, and anxiety in adults with cancer was adapted by ASCO, with some updates to address local US context [62, 63]. A multicomponent survivorship guideline was generated by the NCCN, which provides an overall framework for adult survivorship care, medical late effects and long-term physical and psychosocial problems, and preventive health. However, despite the progress in guideline development, there are inconsistencies in recommendations and omissions of important cancer survivorship domains [64–66].

19.4 Development of Survivorship Programs

Those developing survivorship programs can incorporate guideline suggestions and other evidence-based recommendations, as well as literature on existing survivorship programs that provide evidence-based care [36, 67, 68]. For example, the Livestrong Foundation provided consensus-based

Table 19.2 Examples of adult cancer survivorship guidelines

Guideline	Overview
American Cancer Society	
Breast cancer survivorship guideline (with the American Society of Clinical Oncology)	Recommendations on surveillance for cancer recurrence, screening for second primary cancers, assessment and management of long-term and late effects, health promotion, and care coordination and/or practice implications
Colorectal cancer survivorship guideline	Recommendations on surveillance for cancer recurrence, screening for second primary cancers, assessment and management of long-term and late effects, health promotion, and care coordination and/or practice implications
Head and neck cancer survivorship guideline	Recommendations on surveillance for cancer recurrence, screening for second primary cancers, assessment and management of long-term and late effects, health promotion, and care coordination and/or practice implications
Nutrition and physical activity guideline	Focuses mainly on the needs of disease-free and stable disease survivors, discusses nutrition and activity issues such as weight, food choices, food safety, and dietary supplements
Prostate cancer survivorship guideline	Recommendations on surveillance for cancer recurrence, screening for second primary cancers, assessment and management of long-term and late effects, health promotion, and care coordination and/or practice implications
American Society of Clinical Oncology	
Anxiety and depressive symptoms: an adaptation	All patients should be evaluated for symptoms of depression and anxiety across the trajectory of care, using validated measures and procedures; depending on levels of symptoms, differing treatment pathways are recommended
Chemotherapy-induced peripheral neuropathy	Best available data support a moderate recommendation for treatment with duloxetine
Chronic pain	Clinicians should screen for pain at each encounter and should determine the need for other health professionals to provide comprehensive pain management care in patients with complex needs
Disease-specific guidelines, multiple	Recommendations on surveillance for cancer recurrence, screening for second primary cancers, assessment and management of long-term and late effects, health promotion, and care coordination and/or practice implications
Fatigue in adult survivors of cancer	Regular screening, assessment, and education and appropriate treatment of fatigue are recommended; interventions should be tailored to each patient's specific needs
Fertility preservation	Clinicians should address the possibility of infertility with patients treated during their reproductive years and discuss fertility preservation options and/or refer all potential patients to appropriate reproductive specialists
Integration of palliative care	Recommendations for use of dedicated palliative care services throughout the cancer care continuum for patients with advanced cancer; referral to interdisciplinary palliative care teams is optimal
Prevention and monitoring of cardiac dysfunction	Recommendations for imaging and other services for higher-risk survivors of adult cancer
Children's Oncology Group	
Long-term follow-up guidelines	Recommendations based on exposure-related late effects, with screening and management of survivors of pediatric malignancies
National Comprehensive Cancer Network	
Disease-specific cancer surveillance recommendations	Cancer surveillance recommendations embedded in treatment guidelines; includes schedule of clinician visits and recommended services and screenings
Survivorship guideline	Comprehensive, includes recommendations for cancer surveillance, screening for secondary cancers, screening and management of psychosocial and physical long-term and late effects, and preventive healthcare needs
American College of Sports Medicine	
Exercise guideline for cancer survivors	Recommendations for evaluation, prescription, referral, and use of exercise in survivors

(continued)

Table 19.2 (continued)

Guideline	Overview
International guidelines	
Cancer Care Ontario (Canada)	
Colorectal	Recommendations on surveillance for cancer recurrence, screening for second primary cancers, assessment and management of long-term and late effects, health promotion, and care coordination and/or practice implications
Lung	
Lymphoma	
Prostate	
Sexual problems	Interventions to address sexual problems in people with cancer
Australian Cancer Survivorship Centre guidelines	
Breast	Recommendations on surveillance for cancer recurrence, screening for second primary cancers, assessment and management of long-term and late effects, health promotion, and care coordination and/or practice implications
Colorectal	
Lymphoma	
Prostate	
London Cancer Alliance	
Survivorship guideline	Provides a framework to help healthcare professionals and others implement best practice evidenced-based survivorship care
European Society for Medical Oncology and Spanish Society of Medical Oncology (SEOM)	
Fertility preservation and reproduction	Provides clinical guidelines for fertility preservation and reproduction in cancer patients Disease-specific guidelines thus far have limited content on survivorship but are beginning to include these issues. Supportive care guidelines address toxicities primarily during active treatment
Netherlands Oncoline	
Cancer survivorship cancer rehabilitation	Recommendations for general cancer survivorship care and for rehabilitation after treatment, independent of the type of cancer, with a focus on fatigue, depression, anxiety, limitations in activities of daily living, and social functioning

recommendations (Table 19.3) that provided guidance on the elements that are essential in providing care for cancer survivors. This guidance can provide insights into staffing needs and structure (e.g., core clinical staff, specialist referral network), linkages to clinical services (e.g., imaging and lab services, physical therapy program, psychosocial services), and development of cost and space estimates. In addition, prior reports and guidelines can provide a comprehensive overall structure for survivorship programs and a choice of approach, or program, to fit local context and needs.

19.5 Approaches to Developing a Comprehensive Cancer Center Survivorship Program

In designing a survivorship program within comprehensive cancer centers, where specialty expertise and extended resources provide options for provision of survivorship care, multiple decisions on program components are needed. Some organizations may choose to develop disease-specific programs to address health concerns related to a specific malignancy; others may choose a disease-diagnostic approach that focuses on specific organs or systems affected by cancer or cancer treatment exposure, such as cardiovascular and/or pulmonary survivorship programs for those who receive therapies with known cardiotoxic effects (e.g., trastuzumab, anthracyclines, radiation to the chest) or a program for management of chemotherapy-induced peripheral neuropathy.

More recently, programs are developing hybrid models (see Fred Hutchinson program example described below). Some programs may rely on existing oncology clinicians to provide cancer surveillance and detection of late effects while building supplementary programs to address common post-treatment symptoms such as fatigue or chronic pain, while others collaborate closely with primary care-trained providers [69]. Programs with infrastructure support from

Table 19.3 Essential elements of cancer survivorship care, a consensus statement from a multi-stakeholder meeting convened by the Livestrong Foundation in 2011 (30)

Tier 1 consensus elements: All medical settings ***must*** provide direct access or referral to the following elements of care	*Tier 2 high-need elements*: All medical settings ***should*** provide direct access or referral to these elements of care for high-need patients and to all patients when possible	*Tier 3 strive elements*: All medical settings should ***strive*** to provide direct access or referral to these elements of care
• Survivorship care plan, psychosocial care plan, and treatment • Screening for new cancers and surveillance for recurrence • Care coordination strategy which addresses care coordination with primary care physicians and primary oncologists • Health promotion education • Symptom management and palliative care	• Late effect education • Psychosocial assessment • Comprehensive medical assessment • Nutrition services, physical activity services, and weight management • Transition visit and cancer-specific transition visit • Psychosocial care • Rehabilitation for late effects • Family and caregiver support • Patient navigation • Educational information about survivorship and program offerings	• Self-advocacy skills training • Counseling for practical issues • Ongoing quality improvement activities • Referral to specialty care • Continuing medical education

internal and/or external sources may choose a more comprehensive approach, designing programs to address multiple components of survivorship care using a wide-ranging, multifaceted guideline such as the NCCN survivorship care guideline. Oncology nurses play a critical role in survivorship care, including the program planning and development as well as care delivery. Oncology nurses may be involved in overseeing and delivering cancer surveillance services, preventive care, health education, and symptom management and may design and lead diverse types of survivorship care programs [70].

Survivorship guidelines can also be used to identify gaps in existing post-treatment care programs, to develop program goals, and to highlight areas of need to target for future program development. For example, disease-specific guidelines that provide recommendations for timing and type of post-treatment care (e.g., schedule of physician visits, cancer screening tests, imaging services) can be translated into quality metrics as have been done for several research studies [71, 72]. Alternatively, a cancer survivorship pathway model, such as the National Cancer Survivorship Initiative in the UK, implements risk-stratified survivorship care programs that incorporate disease type, stage, and other relevant characteristics to determine post-treatment care [73].

Measurement of relevant variables and service utilization can be conducted using structured data from electronic medical records, administrative claims, and/or manual chart review or can be built into a clinical informatics dashboard. For example, a breast cancer survivorship program may create a simple dashboard to assess use of recommended annual mammography in eligible breast cancer survivors. Other relevant guidelines, such as those from the *Choosing Wisely* campaign, can be used to measure potential overuse of cancer surveillance services that may not provide benefit and can cause significant harms [74–76]. Local, county, regional, and national results from these evaluations can inform the direction of survivorship program development and adaptation of existing programs to meet population needs. Oncology care guidelines in European countries have focused on diseases or treatment of acute toxicities. However, implementation of rehabilitation programs is far more accessible for cancer survivors than in North America, particularly in Nordic countries, the Netherlands, and Germany [77]. As the evidence base for survivorship care continues to evolve, so will the associated guidelines for care and management of adult cancer survivors. Survivorship care programs can use this growing body of guidelines to develop, manage, and sustain efficient and effective programs

that maximize local resources and ensure optimal outcomes for their patients.

19.6 US National Mandate for Standard Use of a Survivorship Care Plan

Despite consensus about the need for survivorship care and the essential elements for that care, progress in the provision of a treatment summary (TS) and survivorship care plan (SCP) to survivors has remained the exception rather than the rule in comprehensive and community-based cancer centers. This is changing with the mandate from the CoC, which directs all accredited cancer centers in the USA to provide a TS/SCP to all patients completing treatment for an invasive cancer [41]. Based on the current CoC recommendation, by the end of 2018, a minimum of 75% of stage I to III cancer survivors at a CoC cancer center must receive a printed or electronic TS/SCP and have a discussion with some type of provider about the document. The TS/SCP discussion must be within 1 year of diagnosis, by 6 months after treatment, or within 18 months of diagnosis if a patient is receiving long-term hormonal therapy. The CoC accepts the ASCO guidelines as the minimum content elements of the TS/SCP.

The impact of the CoC mandate cannot be overstated in moving survivorship care in the USA from the exception to standard of care. Legitimate challenges in designing, funding, staffing, and determining optimal models for delivery of survivorship care within traditional, treatment-focused cancer centers, lack of an evidence base for best practices, and differences of opinions regarding the utility or effectiveness of these TS/SCPs [78] have restricted the growth and access to these programs for most survivors. However, a decade of experience and research on various models of care delivery, along with survivorship guidelines that establish consensus-based standards, have positioned survivorship experts and cancer centers to implement models of care that suit their settings and meet the CoC standards.

19.7 Application of a Few Models of Care

The IOM report on cancer survivorship recommended the development of specialized cancer survivorship clinics as a potentially effective way to deliver care. However, given the diversity of patient's diagnosis, treatments, and treatment-related side effects, it is not likely that *one-size-fits-all* model will meet the needs of all cancer survivors. What is clear though is that comprehensive, coordinated, and effective programs and models are needed in order to ensure optimal health and recovery following care diagnosis and treatments. Formal cancer survivorship programs have slowly begun to emerge within comprehensive and community cancer centers as well as the community throughout Europe, North America, and Australia, though they differ in terms of their structure, team composition, and the services that they offer [4].

Currently, there are a number of different models of cancer survivorship care which have been categorized using different characteristics including setting (community-based and integrated setting within oncology hospital), patient population (disease specific and general cancer), provider (oncologist, nurse, primary care, shared care), or purpose (transition, rehabilitation) [79–81]. Further, they can be consultative, integrated, or longitudinal in their structure. These models are not mutually exclusive and vary depending on the institution or setting and resources and expertise available. Survivorship care models have yet to be standardized and remain heterogeneous with little evidence on their impact, and there have been numerous calls for more research to inform care and guidelines [79, 82–84]. In a systematic review on models of care for adult cancer survivors, Howell et al. (2012) [84] reported that there is some evidence that primary care- and nurse-led models are equivalent to oncologist-

delivered care, but there is very little evidence on specific models and their effectiveness.

19.7.1 Comprehensive Cancer Centers

While the majority of cancer patients are treated in community-based hospitals, comprehensive cancer centers (CCCs) can play a unique and important role in cancer survivorship given the access to specialized treatments and programs across the care continuum along with their strong research infrastructures and focus on translational research [85, 86]. Organizations such as the Association of American Cancer Institutes (AACI), the Organisation of European Cancer Institutes (OECI), and Cancer Care Ontario (CCO), and the Survivorship Centers of Excellence Network (SCOEN), originally supported by the Livestrong Foundation, can offer unique networks of CCCs that enable sharing of expertise and an infrastructure where new survivorship models of care can be developed, tested, and disseminated.

One of the most established and successful examples is the SCOEN, which was established in 2005 to advance survivorship care and improve the health and quality of life of post-treatment cancer survivors [36]. The network includes seven comprehensive cancer centers, which include leaders in the survivorship field. Over the past decade, the SCOEN has worked to develop and evaluate new interventions for cancer survivors, survivorship best practices, and survivorship care programs and models of care. The SCOEN programs are embedded within CCCs, allowing for the opportunity to promote the survivorship care and potentially influence the culture of oncology practice, as well as providing visibility and leadership for the survivorship community across the cancer care continuum. A unique feature of the network is that each center has designated community affiliate cancer program that works in partnership with the "parent" SCOEN program. Through this partnership, the community affiliates have access to information, research findings, new interventions, as well as expertise and specialist clinicians. Through their community affiliates, the SCOEN benefits by gaining access to patient referrals for those with more complex needs and clinical trial enrollees and also getting information and feedback on cancer survivors' needs and how best to address those needs within the context of their communities.

Over the past decade, many comprehensive cancer centers around the world have developed or are in the process of developing some form of survivorship program and model of follow-up care [3, 87]. These have typically involved one of the three approaches: consultative, longitudinal, and more recently hybrid, risk-stratified models have emerged (Fig. 19.1). The consultative or "consult" model typically involves one or two appointments with a healthcare professional, most often an advanced practice nurse, during which the cancer survivor is assessed, a TS/SCP is developed, and the survivor is provided with tailored resources and referrals to any specialized services as needed. The patient is then followed by their oncology team or transitioned back to their primary care provider, or often both, with an effort to assure coordination of care through delivery of the TS/SCP to the providers and patient.

These consult model programs may be in survivorship-specialized, stand-alone clinics or integrated into disease clinics. In the longitudinal or "long-term follow-up" survivorship model, patients are transitioned from the oncology clinic to a specialized survivorship clinic where they will then receive their follow-up care, and then at some point (often 2–5 years), they will be transitioned back to primary care. Hybrid, risk-stratified models, which have been used in the pediatric cancer population, provide a more personalized approach to survivorship care. These models have developed in recognition that the needs of adult cancer survivors may vary widely based on disease type, treatment exposures, comorbid conditions, and other health needs. As highlighted by van Harten and colleagues [86], given the large number of cancer survivors with heterogeneous needs, it is important to identify those services that are required by each survivor

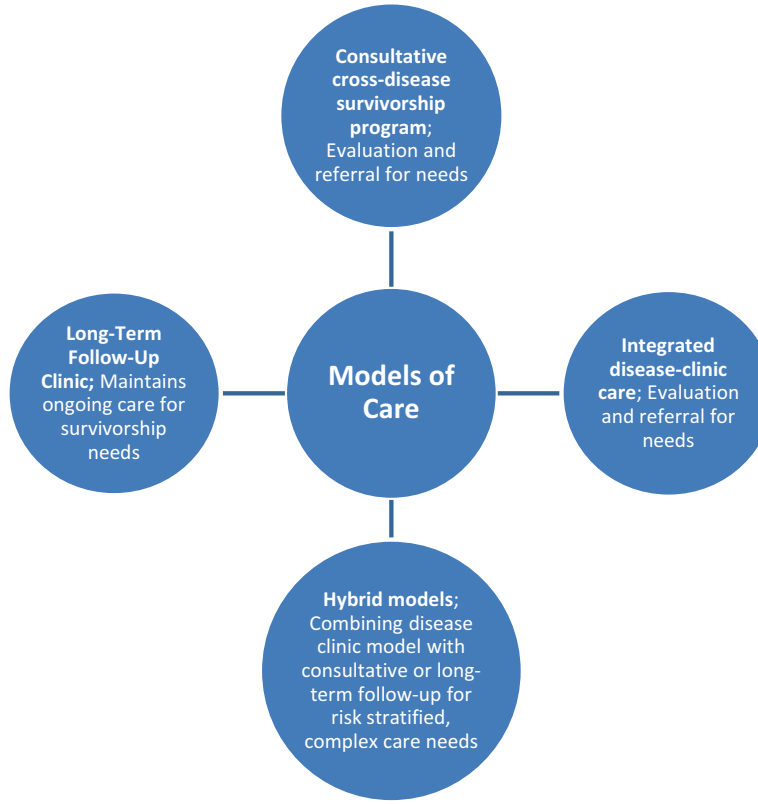

Fig. 19.1 Examples of survivorship care models

and to determine when these services are most effective, or are unneeded, in order to provide patient-centered, cost-effective care. This should also include how often cancer survivors are followed and by whom [88].

Risk-stratified survivorship care models are gaining momentum as survivorship care scales up in accessibility and reach to all survivors and could inform the organization and funding of cancer services. The National Cancer Survivorship Initiative in the UK is leading this approach and has developed clinical pathways informed by electronically collected patient-reported outcomes. These outcomes are used to triage or stratify patients into one of three streams: supported self-management, shared care, and complex case management [89]. The challenge in risk-stratified approaches is the need for an evidence base and brief but sensitive assessment tools that are informative and can be used to assess individual need across a range of outcomes, including treatment exposure late effects and physical and psychosocial functioning. This may include assessment of risk of adverse outcomes (e.g., cardiotoxicity), the magnitude of the risk, and the impact of the risk or risk reduction on the individual [90]. It has been argued that this approach must also consider the availability of effective interventions as well as the health economic implications of managing these risks [90]. In this model, other factors such as time requirements, cost and insurance coverage, and distance from home are also important factors to consider.

An example of an emerging risk-stratified model is the Fred Hutchinson Cancer Research Center (Fred Hutch) in Seattle, with the Seattle Cancer Care Alliance (SCCA) Survivorship Program, one of the SCOEN survivorship programs funded by the Livestrong Foundation (LSF) in 2006. As such, it was an "early adapter" of the consultative model for survivorship care and follows the LSF requirement for three aims of the overall survivorship program: a clinic for

direct delivery of care, education of providers and the broader community including survivors, and research. Adult survivors at the SCCA are seen on referral, which may be provider- or patient-initiated. The initial clinic visit includes a comprehensive online screening of health and psychosocial needs, followed by preparation of a TS/SCP, and then a 60–90-min visit with the survivorship clinician (advanced practice nurse or survivorship physician). The clinician receives a summary of the online patient-reported outcome survey prior to the visit, with highlighting of elevated symptoms, healthcare maintenance needs, or psychosocial concerns along with the TS/SCP. At the visit, the clinician, typically an oncology nurse, other advanced practice nurse, or oncologist, identifies the patient's main concerns, reviews the TS/SCP, uses a self-management shared decision-making process to prepare a road map for future healthcare and immediate action plans with the patient, educates the patient about long-term and late effects, and defines needs for referrals or resources within survivorship collaborators at the SCCA or in the community. As needed, patients may be seen for follow-up consultations at the clinic. However, consistent with its consultative model, the survivorship clinic does not directly provide ongoing healthcare.

All patients are encouraged to maintain non-oncology care with a community primary care provider and to see their oncologist for surveillance needs. These oncology and community providers and the patient receive a copy of the TS/SCP. Patients also receive a notebook of community-based resources and health materials. Referrals are based on individual need, with the most common referrals to nutrition, physical therapy, palliative care, and psychology/psychiatry service within the SCCA. However, the program also has established collaborations with cardio-oncologists, gastroenterologists, social workers, neuropsychologists, and others within the SCCA and University of Washington (UW) rehabilitation and other specialty programs.

The structure of clinical services in survivorship programs has evolved over the past decade through experience and testing of models of care. A key shift is occurring with preparations to meet the CoC mandate and upscale to the volume of visits timed to occur mostly within a year of diagnosis. To meet the needs of the entire SCCA population of stage I to III or hematologic malignancy survivors, the program has initiated a risk-stratified program which begins with a 30-minute, nurse- or nurse practitioner-led visit within 12 to 18 months after diagnosis to review a TS/SCP and personalize the care plan for the individual. At any point in the future, a patient may be referred (or self-refer) to the comprehensive survivorship clinic if elevated needs are identified. Each disease clinic has a choice of delivering the initial TS/SCP visit within their clinic by a disease specialist nurse or having the care provided by a nurse within the survivorship clinic. All disease clinics must meet the ASCO minimum criteria for a TS/SCP.

19.7.2 Role of Cancer Rehabilitation in Cancer Survivorship

The focus of cancer rehabilitation on rebuilding the lives of some people with cancer and maximizing functioning as well as quality of life [91–94]. This aligns very closely with the philosophy of survivorship care and suggests the need to more formally integrate rehabilitation specialists in cancer survivorship care programs and models of care [83]. Rehabilitation programs can fill a gap in survivorship care between the screening, surveillance, and referral focus of most clinics and the need of some survivors for more directed physical and mental recovery care. In the USA, while cancer rehabilitation services experienced some momentum in the late 1970s, it failed to develop in standard survivorship care beyond some specific clinics and services (e.g., lymphedema management) [92, 95].

With the growing number of cancer survivors along with recognition of risk-stratified levels of need, there has been renewed interest in a multidisciplinary cancer rehabilitation approach. It provides an effective model of care with other chronic diseases, including treating persistent and late effects of the disease, managing comorbid conditions, and focusing on prevention [92].

As with survivorship programs, comprehensive cancer rehabilitation programs are the exception rather than the rule. Recent reviews of rehabilitation services available to cancer survivors in the USA [96], UK [97], and Canada [98] demonstrate a scarcity of cancer-specific programs. Most programs operate in large hospitals and cancer centers and are often limited in scope; often patients are referred to non-oncology-specific rehabilitation programs, such as outpatient musculoskeletal clinics or community-based clinics [98]. Scandinavian and European countries are further ahead and have begun to develop and implement cancer rehabilitation programs [77] that can provide models on which others can build upon. In Canada, only about 1/3 of cancer centers offer some form of oncology rehabilitation program.

The Princess Margaret Cancer Centre offers Canada's only integrated Cancer Rehabilitation and Survivorship (PM CRS) program. Since its inception in 2005 in the breast site (Breast Cancer Survivorship Program), the program has evolved to include a large dynamic multidisciplinary team (including program and patient coordinators, physiatrist, physiotherapists, occupational therapists, dietician, wellness chef, neuropsychologist, social worker, massage therapists and kinesiologists, as well as a large research team) that now provides consultative risk-stratified impairment-driven care to all disease sites. Based on the level of complexity and disability as well as patient goals of care, a care plan is developed in which the patient is triaged to one of three streams: (1) internal and community-based wellness and patient education resources and programs, (2) CRS services, and/or (3) specialized services (i.e., pain clinic, falls prevention, MSK rehabilitation service). The CRS services include a group-based lymphedema clinic, one-on-one consults (i.e., physiatry, physiotherapy, neurocognitive, sexuality, nutrition, return to work), and an innovative multidimensional 8-week structured group cancer rehabilitation program (Care@ELLICSR) that includes both exercise and supported self-management classes. An online version of the 8-week program Care@Home will be launched in 2018.

In the USA, the majority of US National Cancer Institute-designated cancer centers currently do not have comprehensive cancer rehabilitation programs. However, despite geographical distances to services or lack of health insurance coverage, cancer rehabilitation pilot programs are beginning to emerge in the USA. A handful of centers of excellence exist including MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, the Rehabilitation Institute of Chicago, and the Mayo Clinic. Each of these programs varies in their offerings with respect to inpatient and outpatient services, interventions offered by rehabilitation medicine, and the overall focus of rehabilitation medicine. It is also not clear how integrated these programs are with other survivorship initiatives in their centers. Perhaps in the future, cancer survivorship and cancer rehabilitation programs will be integrated and coordinated rather than working in siloed practices. Barriers to the development of oncology rehabilitation programs include lack of public funding, uncertainty regarding consistent and sufficient reimbursement for bundled services seen in these programs, limited evidence of demand for such programs by cancer survivors, and insufficient evidence for its long-term cost-effectiveness.

19.8 Future Directions

Over the past decade, survivorship care has moved from inception and testing of various models of care, with a small evidence-based platform from which to build programs, to a larger research base and a wealth of experience in developing and delivering care to post-treatment cancer survivors. With the progress from both research and clinical care implementation testing, survivorship programs are now providing varying models of care that share some core features. Within CCCs, as seen with the examples described, central features include (1) risk-stratified determination of need through online delivery of assessments after completion of treatment; (2) efforts to provide TS/SCP by a clinician, with discussion of the survivorship road

map, to most if not all survivors of invasive cancers treated with curative intent; (3) either on-site rehabilitation services for those needing more extended recovery care or referral to local specialists and services for recovery care or surveillance and treatment of long-term and late effects. Partnership with CCCs may allow community-based cancer programs that do not have access to diverse local expertise to benefit from either linked services or referrals for higher-risk patients with specialized needs.

Creating new programs and innovative models of care incorporating the IOM report recommendations, the expanding universe of survivorship guidelines, and other sources (e.g., the CoC accreditation standards) may present an overwhelming array of options. Program developers must consider the acceptability, feasibility, and effectiveness of implementing these recommendations in the context of their care delivery system.

Prioritizing elements of program development can be based on pre-implementation planning, needs assessment surveys, clinician and administrative expertise, and patient and other stakeholder engagement. Determination of essential program elements may vary across programs; some will be able to leverage existing resources, such as a behavioral health program, or will partner with local agencies and organization to deliver components of care, such as a physical activity program. Other drivers may influence survivorship program development and sustainability, including survivor and community-wide advocacy, institutional support, payor incentives, financial sustainability other than the government or insurance industry, cost-effectiveness, and organizational leadership goals.

Several issues remain to be resolved as survivorship programs continue to refine their delivery of care. Although all programs strive to meet the needs of all their survivors, none that we are aware of have fully achieved this goal. Three methods may facilitate achieving delivery of the right level of care to each interested survivor at the key points of need: (1) use of technology to provide cost-effective mechanisms for improving the reach of survivorship care, including online screening (e.g., post-treatment symptom assessment), delivery of education and follow-up care, and preparation of the TS/SCP; (2) use of risk-stratified models for determining expertise needed and time required for clinic visits or rehabilitation care will help to assure that resources are used optimally, targeted to where they are needed; and (3) use of group formats, either in-person or online, will help to ease some of the resource limitations and access issues that many survivorship programs and their patients face.

Within this next decade, we envision further improvement in high-quality cancer survivorship care, with all cancer survivors receiving the services they need at the time point those needs arise and at a location that is accessible and reduces travel burden. An emerging challenge is integration of survivorship care planning earlier in the continuum of care, so that planning for long-term health begins at diagnosis. A second challenge that demands our attention is the testing of various models of care for the growing number of cancer survivors living with long-term disease or offering preventive approaches (e.g., exercise) for the remainder of their lives. Finally, we recognize a continuing need to refine follow-up processes that recognize that survivors' needs change over time, as does the science underpinning the survivorship care that we provide.

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International Perspectives

20

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20.1 Introduction

Currently there are 32.6 million cancer survivors around the globe, including individuals from the World Health Organization (WHO) regions in Africa, the Americas, Eastern Mediterranean, Europe, Southeast Asia, Western Pacific, the International Agency for Research on Cancer (24 countries), the United States, China, India, and the European Union. In the same period, in developing countries, there were 15.6 million individuals who were 5-year cancer survivors [1, 2]. Lung cancer was the most common cancer worldwide contributing 23% of the total number of new cases diagnosed in 2012. Breast cancer (women only) was the second most common cancer with nearly 1.7 million new cases in 2012 [3]. Table 20.1 illustrates the estimated global cancer prevalence for adults (15 years and older) by geographic area, level of the area's development, and sex [4]. The table shows a greater percentage of people living with and beyond cancer from the very high Human Development Index (HDI)[1] areas compared to those in the low and medium HDI areas; overall, the global prevalence was estimated to be 28.8 million in 2008 diagnosed with cancer within the last 5 years.

The overall age-standardized incidence of cancer, as illustrated in Fig. 20.1, is nearly 25% higher in men than in women [2]. It varies by regions of the world with incidence rates for men ranging from 79 per 100,000 in Western Africa to 365 per 100,000 in Australia/New Zealand. Incidence in females is not as widely ranging with rates from 103 per 100,000 in South-Central Asia to 295 per 100,000 in Northern America. Although progress is being made, cancer survivorship with respect to care provision and the shifting of healthcare policy, it remains a significant health burden internationally with survivorship not yet even attainable for some countries because of a number of socioeconomic, cultural, and environmental factors.

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[1]The Human Development Index (HDI) is a statistic that is composed of life expectancy, education, and income per capita indicators. A high HDI indicates that a country has a high life expectancy at birth, a longer period of education, and a higher income per capita.

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Table 20.1 Estimated global cancer prevalence in adults, 2008

		Population size		5-year prevalent cases (in thousands)					5-year prevalence proportions (%)		
Area	HDI (range)	In thousands	%	Both sexes	%	Males	Females	M:F ratio	Both sexes	Males	Females
Sub-Saharan Africa	0.340–0.930	446,440	9.1	1109.4	3.9	412.9	696.5	0.6	0.25	0.19	0.31
Middle-East and Northern Africa	0.531–0.935	291,204	5.9	817.8	2.8	356.0	461.8	0.8	0.28	0.24	0.32
Latin America and Caribbean	0.532–0.930	411,861	8.4	2145.8	7.4	950.0	1195.8	0.8	0.52	0.47	0.57
Northern America	0.956–0.966	275,749	5.6	4696.1	16.3	2395.1	2301.0	1.0	1.70	1.78	1.63
Eastern Asia	0.676–0.960	1,259,090	25.6	7055.2	24.5	3490.8	3564.4	1.0	0.56	0.55	0.58
South-Eastern Asia	0.489–0.944	414,319	8.4	1440.9	5.0	522.1	918.8	0.6	0.35	0.26	0.44
South-Central Asia	0.352–0.804	1,172,793	23.9	2682.4	9.3	993.8	1688.6	0.6	0.23	0.17	0.29
Central and Eastern Europe	0.720–0.903	250,335	5.1	2289.0	7.9	985.2	1303.8	0.8	0.91	0.85	0.97
Northern Europe	0.866–0.971	80,784	1.6	1235.2	4.3	593.8	641.4	0.9	1.53	1.51	1.54
Southern Europe	0.812–0.955	130,147	2.6	1940.5	6.7	1012.1	928.4	1.1	1.49	1.60	1.38
Western Europe	0.947–0.964	157,878	3.2	2999.4	10.4	1596.3	1403.1	1.1	1.90	2.09	1.72
Australia/New Zealand	0.950–0.970	20,387	0.4	371.6	1.3	199.3	172.3	1.2	1.82	1.99	1.67
Oceania		5982	0.1	19.6	0.1	7.4	12.2	0.6	0.33	0.25	0.41
Very high human development[a]	0.902–0.971	835,216	17.0	13605.7	47.2	7068.8	6536.9	1.1	1.63	1.73	1.53
High human development[b]	0.804–0.895	700,425	14.2	4386.1	15.2	1932.8	2453.3	0.8	0.63	0.57	0.68
Medium human development[c]	0.511–0.935	3459,839	64.3	10325.9	35.8	4335.8	5990.1	0.7	0.33	0.27	0.38
Low human development[d]	0.340–0.499	219,437	4.5	480.3	1.7	175.4	304.9	0.6	0.22	0.16	0.27
More developed regions	0.720–0.971	1,025,464	20.9	15262.0	53.0	7756.1	7505.9	1.0	1.49	1.58	1.41
Less developed regions	0.340–0.944	3,891,505	79.1	13541.1	47.0	5758.7	7782.4	0.7	0.35	0.29	0.40
World	**0.340–0.970**	**4,916,969**	**100.0**	**28803.1**	**100.0**	**13514.8**	**15288.3**	**0.9**	**0.59**	**0.55**	**0.62**

Source: Bray et al. [4]

[a]Very high HDI: Australia; Austria; Barbados; Belgium; Brunei Darussalam; Canada; Cyprus; Czech Republic; Denmark; Finland; France (metropolitan); France, Guadeloupe; France, La Reunion; France, Martinique; French Guyana; French Polynesia; Germany; Greece; Iceland; Ireland; Israel; Italy; Japan; Korea, Republic of Kuwait; Luxembourg; Malta; New Caledonia; New Zealand; Norway; Portugal; Qatar; Singapore; Slovenia; Spain; Sweden; Switzerland; Taiwan; The Netherlands; United Arab Emirates; United Kingdom; United States of America

[b]High HDI: Albania; Argentina; Bahamas;– Bahrain; Belarus; Bosnia Herzegovina; Brazil; Bulgaria; Chile; Colombia; Costa Rica; Croatia; Cuba; Ecuador; Estonia; Guam; Hungary; Kazakhstan; Latvia; Lebanon; Libya; Lithuania; Macedonia; Malaysia; Mauritius; Mexico; Montenegro; Oman; Panama; Peru; Poland; Puerto Rico; Romania; Russian Federation; Saudi Arabia; Serbia; Slovakia; Trinidad and Tobago; Turkey; Uruguay; Venezuela

[c]Medium HDI: Algeria; Angola; Armenia; Azerbaijan; Bangladesh; Belize; Bhutan; Bolivia; Botswana; Cambodia; Cameroon; Cape Verde; China; Comoros; Djibouti; Dominican Republic; Egypt; El Salvador; Equatorial Guinea; Fiji; Gabon; Georgia; Ghana; Guatemala; Guyana; Haiti; Honduras; India; Indonesia; Iran, Islamic Republic of Iraq; Jamaica; Jordan; Kenya; Korea, Democratic People Republic of Kyrgyzstan; Lao People's Democratic Republic; Lesotho; Madagascar; Maldives; Mauritania; Moldova; Mongolia; Morocco; Myanmar; Namibia; Nepal; Nicaragua; Nigeria; Pakistan; Palestine; Papua New Guinea; Paraguay; Philippines; Republic of the Congo; Samoa; Solomon Islands; South Africa; Sri Lanka; Sudan; Suriname; Swaziland; Syrian Arab Republic; Tajikistan; Tanzania; Thailand; Tunisia; Turkmenistan; Uganda: Ukraine; Uzbekistan; Vanuatu; Viet Nam; Western Sahara; Yemen

[d]Low HDI: Afghanistan; Benin; Burkina Faso; Burundi; Central African Republic; Chad; Cote D'lvoire; Democratic Republic of the Congo ; Eritrea; Ethiopia; Guinea; Guinea–Bissau; Liberia; Malawi; Mali; Mozambique; Niger; Rwanda; Senegal; Sierra Leone; Somalia; The Gambia; Timor–Leste; Togo; Zambia; Zimbabwe

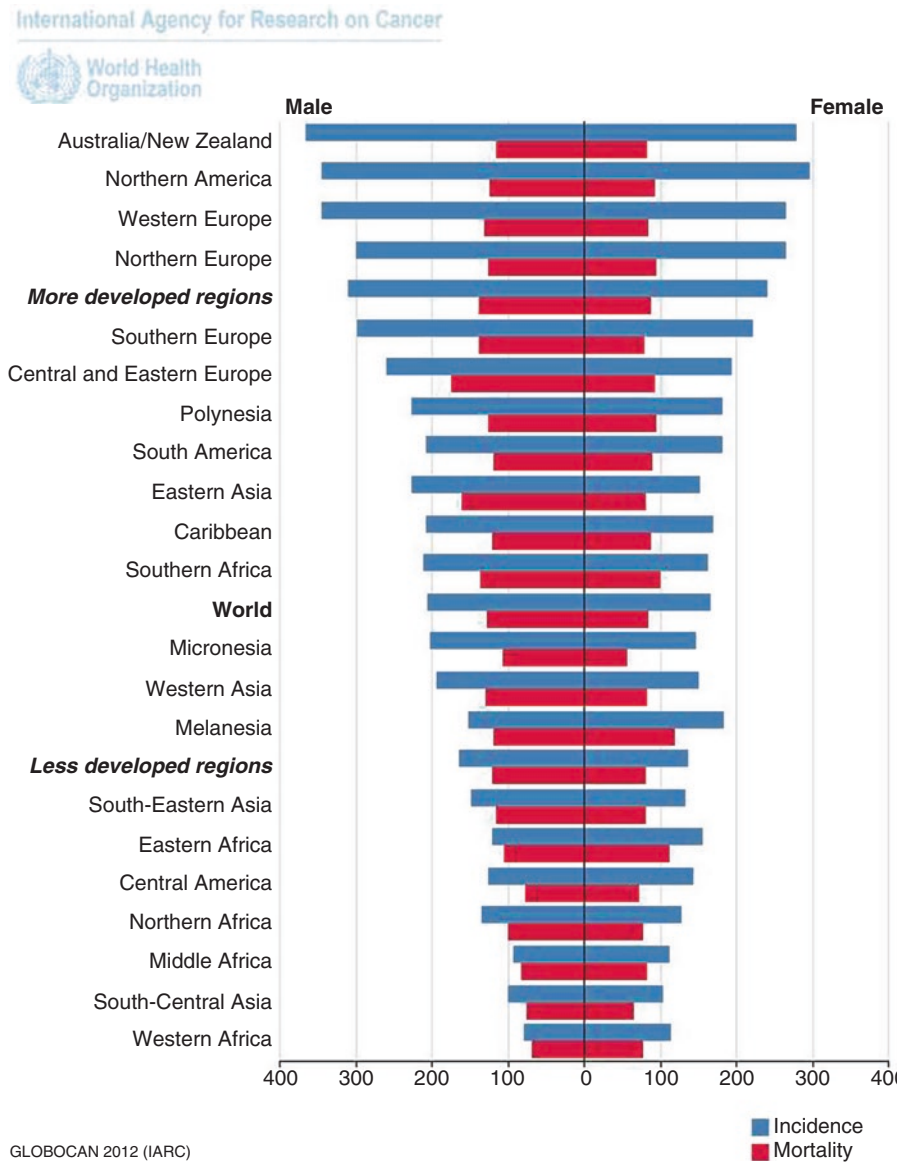

Fig. 20.1 Estimated age-standardized rates (world) per 100,000. (Source: Ferlay et al. [2])

20.2 Defining Cancer Survivorship Globally

The criteria used to determine the number of cancer survivors in various nations is highly variable. Some use prevalence figures (i.e., ever diagnosed and still alive), while others use measures such as 5-year survival or longer. Prevalence is impacted by incidence and the success of treatment. These factors complicate "survivorship data" as some countries are better at detecting and recording cancers, while others are better at treating cancers; global variations occur in both detection and treatment. This is particularly important when considering the global burden of cancer survivorship.

The main source of international cancer statistics is the International Agency for Research on Cancer (IARC). In 1975, this agency began estimating the burden of incident cancer cases for 12

common forms of cancers throughout the 24 different countries where the United Nations collects data [5]. These forms of cancer included the mouth/pharynx, esophagus, stomach, colon/rectum, liver, bronchus/lung, breast, cervix, prostate, bladder, lymphatic tissue, and leukemia. Since the 1960s, individual countries have collected registries on their populations; however, this was accomplished without little coordination or intent to collaborate among nations.

Overall differences in survival rates have been attributed to variables such as stage at cancer diagnosis, the availability and quality of healthcare services, the type of cancer care received, and the follow-up care received, if any. There are also individual level variables that can contribute to the variation in survival rate including socioeconomic status, attitudes and beliefs about treatment, and adherence to treatment recommendations [6]. Thus far, the IARC has observed that individuals with head and neck, large bowel, breast, melanoma, cervix, ovary, and urinary bladder are more likely to survive following cancer diagnosis. Early detection remains the greatest factor to influence survival in those cancers [7]. 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. With current information technology, resources could be used to generate a true global registry of survival and survivorship.

20.3 International Cancer Health Systems

Much of what contributes to healthcare for cancer survivors depends upon the healthcare system and the economic environment within which the individual must interact [8]. Healthcare systems vary across nations, as does the economic infrastructure of the nations themselves [8]. An understanding of the political situation at any given time and the healthcare system of a country is considered an important factor to develop, refine, and sustain research, treatment, and ongoing care of cancer survivors [9].

Canada, Australia, and most of the European countries do not attach health insurance to employment; therefore, losing a job does not mean the individual loses his or her health insurance [10–13]. Most of the European countries offer free universal healthcare coverage subsidized by tax revenues. The provision of quality care for both the rich and the poor, at minimal or no cost, is a goal of the healthcare systems in the United Kingdom, Germany, France, Denmark, and Norway [9]. Conversely, nations without such economic resources and organized healthcare may be in weaker positions to address cancer survivorship care and all the medical and psychosocial issues that it entails [9].

Providing funding is only part of the healthcare challenge. In Bangladesh and Nepal, despite increases in governmental funding to a number of healthcare facilities, the overall utilization rate of these resources remains low as there is a negative perception of healthcare quality in those public facilities [14]. It has also been reported that in China, India, and Thailand, there is a large variation in cancer survival rates related to the level of the countries' development and access to healthcare services. This variation is more pronounced in urban compared to rural settings where access to resources varies [15]. This issue of survival impacted by healthcare infrastructure as well as availability of providers has also been noted in sub-Saharan Africa, Central America, and certain countries in Asia [16]. Overall, it is clear that a country's health system organization, availability of health professionals, and adequate support to provide quality care are fundamental to ongoing care which impact the number of cancer survivors and their long-term outcomes.

International cancer control is varied and based on many components including factors such as geography, growing and changing economies, the aging of populations, the increased adoption of Western lifestyles, marginalized subpopulations, and the physical environment itself, all of which impact cancer treatment and ultimately cancer survivorship [17]. For example, China experiences problems related to access to care, a belief that a cancer diagnosis is always fatal, and the fre-

quent use of traditional medicine over evidence-based medicine as first-line cancer care [18]. India has problems with the affordability of healthcare, the lack of health providers, and sociocultural barriers [19]. India also has found that cancer diagnosis and treatment are becoming increasingly unaffordable because cancer care has focused on expensive diagnostic and imaging services and on specialized treatments and costly medications [20]. These barriers negatively influence cancer treatment, thus limiting chances at survivorship. Russia also copes with the impact of inconsistent access to care, inequitable treatment once accessed, the need for greater scientific rigor in its medical care and research, and the need for improved international collaboration to help control cancer [17]. Collectively, China, Russia, and India represent half of the international cancer burden (i.e., 46% of all new cancers worldwide, and account for 52% of cancer deaths globally). These countries face sociopolitical, cultural, and environmental factors that impact cancer control and, in turn, cancer survivorship [21].

The WHO is working to address cancer globally and to specifically support the developing nations, partnering with NGOs in each nation as possible. The WHO is following steps internationally where developed nations have taken to refocus worldwide healthcare on chronic noncommunicable diseases such as cancer, to shift the focus from acute and episodic care, and to manage longer-term chronic illness.

The WHO is also seeking to reduce fragmentation in care delivery, particularly as the care of the chronically ill often can benefit from a different focus than acute care and benefits from coordination and integration between settings, providers, and across time [22]. Reducing this fragmentation has been shown to improve health, decrease waste and inefficiency, and be less trying on patients needing to navigate these systems [23]. Additionally, the WHO understands the value of the patient and the family working together in the care of the chronically ill [23]. The WHO also 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 [23].

20.4 Needs of Cancer Survivors

Survivors can experience a broad range of consequences following cancer and cancer treatments. These effects seem to occur regardless of country and have been reported to include symptom burden (pain, fatigue, and depression), impaired function, financial instability, poorer overall quality of life, and contribute to premature death. Numerous studies, although predominantly from developed countries, suggest that the care of survivors after initial treatments remains suboptimal [24–26]. Although improvements have been made, there continues to be a limited awareness of the impact of the diagnosis and treatment can have on the "survivor experience" [27]. While increased efforts to prevent, detect, and respond to these long-term and late effects have emerged over the past decade [28], significant challenges persist as many chapters of this book highlight.

20.5 Cancer Survivorship Programs Internationally

Following the establishment of registries to help quantify the actual numbers in their populations with various cancers, many countries have begun to develop comprehensive cancer care centers (e.g., Sweden, France, and Germany). Understandably, most are directed at cancer diagnosis and treatment, slowly broadening their focus to include cancer survivor services in their care networks. Comprehensive cancer control includes a focus on planning, monitoring and surveillance, prevention, screening and early detection, treatment, cancer survivorship care, and palliative care [29]. The WHO recognizes that, based on resources, countries will prioritize different aspects of comprehensive cancer control. It is important now to take a look globally to see what is occurring within both developed and developing countries to related to cancer survivorship [30].

There are countries that have significantly progressed in the areas of cancer survivorship research and practice [31]; however, the efforts are uneven in the types and breadth of services and a specific emphasis on program development for future improvement. The following section will provide a snapshot of what certain countries are focused on when it comes to cancer survivorship. We also emphasize how the programs interact or supplement existing efforts within the healthcare systems or available resources in various nations. It is important to note that our review is not meant to be comprehensive. Providing an overview of all programs around the world is beyond the scope of this chapter.

20.5.1 Europe

United Kingdom Countries included in the United Kingdom each have a universal, publicly funded National Health Service (NHS) or equivalent. In addition, there is a relatively small private health system. NHS improvement has been working as part of the National Cancer Survivorship Initiative (NCSI) to enhance the quality and effectiveness of care and support to those living with and beyond cancer. The NCSI was established as a recommendation arising from "The Cancer Reform Strategy (2007)" and has been furthered by the work in the "Improving Outcomes: a Strategy for Cancer" (2011) [32]. NCSI was a partnership between a national charity, Macmillan Cancer Support, the English Department of Health, and the quality improvement agency NHS Improvement [33]. NCSI led significant work to improve posttreatment survivorship care [31]. This work includes a shift from moving from a more medical focus to an approach that uses individualized care based on the survivor's needs and preferences to promote recovery, health, and overall well-being [34]. Efforts over the past several decades have seen improvements in cancer survivorship in the United Kingdom, demonstrating that the healthcare system has developed some successful understanding of the needs of cancer survivors for their care post-cancer treatment [35]. There has been a progressive rollout of the "recovery package," which includes holistic needs assessment and care planning, delivery of a treatment summary, health and well-being events for survivors, and cancer care review appointments in primary care. England is also progressively rolling out stratified models of care, including shared care between cancer specialists and primary care providers [31, 36]. Figure 20.2 illustrates the model of care called living with cancer, which includes principles of the recovery package in care pathways applied to all ages of cancer survivors.

The NCSI has supported the implementation of breast, colorectal, and prostate stratified pathways in sites across the NHS and the implementation of stratified pathways following treatment benefits patients, healthcare providers, and the NHS (32) with outcomes to include (1) an improvement in survivors' experience and patient-reported outcomes of care from baseline, (2) a 50% reduction in outpatient attendance from the traditional model, and (3) a 10% reduction in unplanned admissions from baseline [32, 37]. Figure 20.3 outlines the five shifts suggested by the National Cancer Survivorship Initiative for England Vision.

Germany also has seen an increase in cancer incidence, particularly in the breast, prostate, colorectal (large bowel), lung, and bladder [38]. It is estimated that 51% of men and 43% of women will develop cancer during their lifetime. Germany's healthcare payment system does allow patients the legal right to an inpatient or outpatient rehabilitation program usually lasting 3 weeks and it extends to assist with work reentry for cancer survivors [39].

Germany has seen positive cancer care outcomes over other Organization for Economic Cooperation and Development (OECD) countries with lorger survival and lower mortality rates [40]. Healthcare in Germany is universal regardless of income, social status, age, gender, or insurance status [40]. Their approach to cancer care is based on evidence-based guidelines and in certified cancer centers. While the National Cancer Plan [41] addresses cancer control and care including rehabilitation, there is no explicit policy on cancer survivorship. There is an aware-

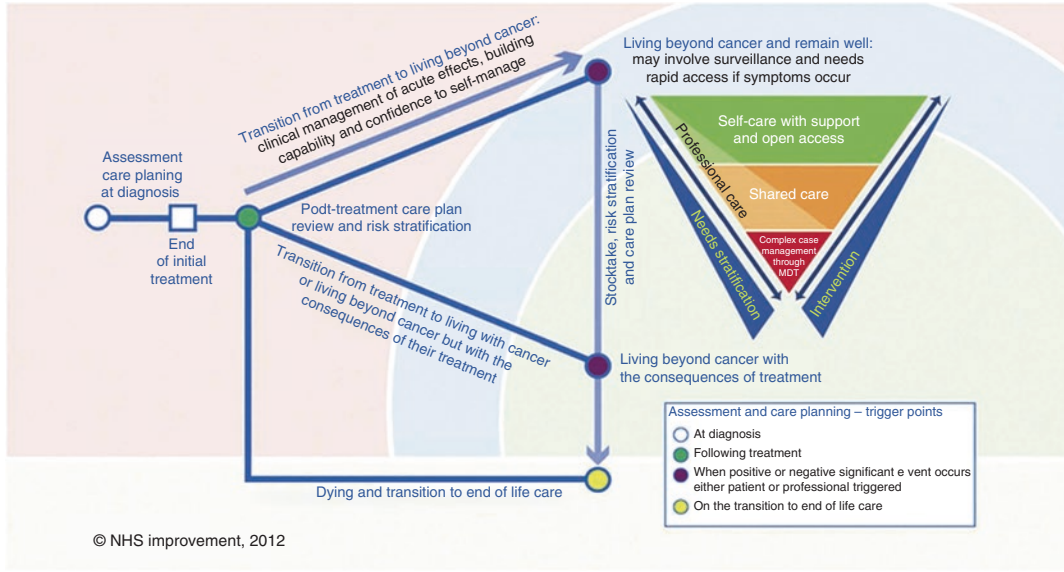

Fig. 20.2 Illustrates the model of care: living with and beyond cancer. (From: Jefford et al. [31])

The National Cancer Survivorship Initiative for England Vision enumerated five shifts in care and support for people living with and beyond cancer:

1. A cultural shift in the approach to care and support for people affected by cancer– to a greater focus on recovery, health and well-being after cancer treatment.

2. A shift towards holistic assessment, information provision and personalised care planning. This is a shift from a one-size fits all approach to follow-up to personalised care planning based on assessment of individual risks, needs and preferences.

3. A shift towards support for self-management. This is a shift from a clinically led approach to follow-up care to supported self-management, based on individual needs and preferences. This approach empowers individuals to take on responsibility for their condition supported by the appropriate clinical assessment, support and treatment.

4. A shift from a single model of clinical follow-up to tailored support that enables early recognition of the consequences of treatment and the signs and symptoms of further disease as well as tailored support for those with advanced disease.

5. A shift from an emphasis on measuring clinical activity to a new emphasis on measuring experience and outcomes for cancer survivors through routine use of patient-reported outcome measures in aftercare services.

Source: Richards, M., Corner, J., & Maher, J. (2011). The National Cancer Survivorship Initiative: new and emerging evidence on the ongoing needs of cancer survivors. Br J Cancer. *105*(Suppl 1), S1-S4.

Fig. 20.3 National Cancer Survivorship Initiative for England Vision. (Source: Richards et al. [79])

ness that information needs to be collected on survivors' quality of life after the acute treatment phase has been completed, and this information was added to the national comprehensive cancer registry which began in 2013 for federal states of Germany [41] with an additional element added in September 2016 to identify gaps in care at all stages of the care continuum. Germany currently does not have a patient-centered approach to cancer survivorship. It has been reported that general practitioners need more information on support and information related to cancer survivorship [42].

Nordic Countries For almost a century, there has been public paid healthcare in the Scandinavian countries (Denmark, Finland, Iceland, Norway, and Sweden) having almost 23 million inhabitants supported by a tax system which on average requires citizens to pay some 50% of their income to the public budget covering kindergartens, schools at all levels, universities, and public healthcare from the general practitioner to the advanced, highly specialized clinical departments at hospitals. Like many countries, follow-up has tended to be specialist led and largely focused on the detection of cancer recurrence.

Denmark has implemented cancer care programs to address the multifaceted needs of the cancer patient called the "shared cancer care program" and tested in Denmark whereby the responsibility for the long-term healthcare follow-up of the cancer patient is to be shared between individuals or teams [43]. 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.

This shared care program has 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. The program also involved professional training, the buy-in of primary care practitioners to broaden their role to assist with direct follow-up of the oncology care, and reimbursement.

A randomized control trial was used to place patients into an intervention or a control group [44]. The project required completion of a treatment summary and care plan. The main outcome measures addressed health-related quality of life and patients' attitudes toward their healthcare services. Although no significant differences were found regarding health-related quality of life between the treatment and the control group, evaluation of patients' attitudes about the program indicated that patients reported that the treatment approach was successful in terms of patients' feeling less like they were in "limbo" and feeling a sense of collaboration among the professionals working with them; patients were more likely to contact their general practitioners with questions than controls. The researchers reported this shared care program had particular benefit for young patients and with men.

With this fact in mind and one trial showing a limited effect of survivorship care plans [45, 46], the Scandinavian health authorities have been focused on the transition between the secondary sector (i.e., oncology department) and the general practitioner as these transitions have been most difficult for patients to cope with. In addition, even in those countries with free access to healthcare at all levels, substantial social inequalities exist with regard to both survival and adherence with lifestyle recommendations to cancer survivors [47, 48]. While social factors are often investigated by race (in addition to education and income) in the United States, this is not the case in most European countries (350 million inhabitants) where populations have traditionally been more racially homogenous.

It is expected that the current immigration situation will influence the cancer pattern with regard to risk and incidence over the decades to come. Factors such as living alone, having minimal formal education, and comorbidity prevalent at time of diagnosis of a cancer can result in certain cancer survivors with poor prognoses. This group of patients presents the most recent significant challenge in the Scandinavian and European context. Survivorship care plan "think-

ing" is more in the direction of what self-care and what responsibilities may be expected from the public health system. Going forward, European countries will need to examine disparities in cancer survivorship care as well as develop models of care that may be acceptable to a more diverse patient population.

Models sharing the care duties between the health system and the individual and between the doctor and the nurse and stratifying by both comorbidity and social situation will probably become new paradigms in the public paid health systems in the Nordic countries in order to overcome and address the challenges of the large number of aged survivors of many types of chronic diseases including cancer.

20.5.2 North America Excluding USA

Canada Canada has made some modifications in their cancer care programming to increase the use of primary care over specialists for survivorship care, to reduce reliance on more expensive specialists, and to move ongoing care into the community. Cancer centers in Canada have recognized this important role and have intervened to support the role of the family practitioner [49], 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 and refine communication between these two professionals to enhance patient care. Most recently, Canada has established a Pan-Canadian Framework for Cancer Survivorship Research [50]. The Canadian Cancer Research Alliance (CCRA) is comprised of Canada's major cancer research funders who work to advance cancer research in Canada.

Identified research domains and crosscutting themes have very broad applicability; themes include engagement of survivors, special populations, knowledge to practice, and capacity building and infrastructure all focused on the development of a survivorship research framework as one of the CCRA's main goals (the other goal is focused on palliative and end-of-life care). The framework was developed through a strategic literature review, a critical analysis of the research funding available for cancer survivorship, and by information gathered from the survivorship stakeholder community through key informant interviews and an online survey [50]. Their work was part of the *Target 2020*, the CCRA's strategic plan to promote shared and targeted research investment. The following are the Pan-Canadian Framework for Cancer Survivorship Research goals focusing on understanding the experiences of survivors, understanding more about late effects, and examining different approaches or models of care [50]:

1. Ensure ongoing and meaningful involvement of cancer survivors and their family/friend caregivers
2. Align funding calls with existing needs and potential for impact
3. Create opportunities for the translation of research into practice and policy
4. Build and maintain infrastructure and expertise to advance research

20.5.3 Australia

Major strides have been taken in Australia to focus the treatment of the cancer patient through the use of a multidisciplinary model of care (including the patient's general practitioner) along with key significant others. Australia also has a publicly funded universal healthcare system and a parallel private healthcare system. In the publicly funded system, many of the principles espoused by United Kingdom's NCSI are shared. For example, risk stratified pathways of care and a shift to greater delivery and engagement with primary care have been implemented [31]. Also, similar to other universal healthcare systems, there are goals of cost containment and efficient use of limited healthcare resources. Currently, the dominant model of posttreatment care is specialist led, with an emphasis on detection of

Enablers	Challenges
Individual Level	
Preparation of survivors for the post-treatment care	Terminology around 'survivorship'
	Flexibility of approaches within programs
Organizational Level	
Receptivity and awareness of survivorship issues within acute health service	Identification and capture of survivors at end of treatment
Clinical leadership and strong project teams	Survivorship care plans
	Sustainability beyond project phase
System Level	
Workforce education and training	Terminology
Existing relationships with primary care	Implementing needs assessment and risk stratification
Collaborations with community providers including non-government organizations	Engagement with primary care
	Gaps in services for survivors
	A shift to self-management and wellness

Fig. 20.4 Enablers and challenges to implementing new models in Australia of posttreatment care. (Adapted from Jefford et al. [37])

cancer recurrence, rather than more holistic, coordinated whole of person care.

A number of states have explicit goals and programs of work regarding survivorship care embedded within state-based cancer control plans. Victoria, the country's second most populous state, launched the Victorian Cancer Survivorship Program (VCSP) in late 2011 with funding from the Victorian state government through the Department of Health and Human Services [51]. Like the NCSI in England, VCSP has a population focus. Figure 20.4 depicts the challenges, enablers, and barriers from the first phase of the VCSP that were likely to contribute to the ongoing development of survivorship models and have international relevance [37].

The Clinical Oncology Society of Australia (COSA) (a multidisciplinary professional organization) has developed a "Model of Survivorship Care: Critical Components of Cancer Survivorship Care in Australia Position Statement," though this has not yet been implemented or evaluated [52]. This plan utilizes three pillars to establish the cancer survivorship plan using cancer survivors, the community, and healthcare professionals (primary and specialists) as those pillars [53]. Figure 20.5 illustrates the pillars and the care responsibilities attached to each.

Cancer Australia, the major national government agency working to reduce the impact of cancer on all Australians, has developed "Principles of Cancer Survivorship," which provide a national framework to guide policy, planning, and health system responses to cancer survivorship, focusing on the health and well-being of people living with and beyond cancer [54]. Cancer Australia has supported the evaluation of models of shared care for cancer patients and survivors.

There is considerable research activity in Australia related to cancer survivorship [55], though no national research agenda. This research may shape the delivery of survivorship care. For example, a randomized study evaluated the efficacy and feasibility of shared care for survivors of prostate cancer and found that such care for low to moderate risk prostate cancer survivors is feasible and appears to produce clinically similar outcomes to those of standard care, at a lower cost [56]. Another study evaluating the implementation of a nurse-led telephone-based diet and exercise intervention (delivered through cancer charities) may lead to a novel, sustainable model of care [57].

Survivorship Care		
Surveillance, Education, Coordinated Care, Advocacy		
Survivor	**Community**	**Health Professionals** *Primary & Specialist care*

Surveillance
• Self-Management
  ○ Care Plan
• Self-monitoring signs & symptoms
• Attend check ups
	Surveillance
	• Self-Management
	• Self-monitoring signs & symptoms
	• When & where to seek support
		Surveillance
		• Screening & assessment for:
		  ○ Cancer
		  ○ Other chronic conditions
		  ○ Physical & psychosocial issues

Engagement • Motivation to change • Self, family, social group • Education • Self, family, social group	**Engagement** • Motivation to change • Education • Support groups • Psycho-educational programs • Online support tools	**Engagement** • Motivation to change • Education • Goals of care • Wellness

Multidisciplinary Collaborative Care
• Self-management:
• Physical
• Psychological
• Social
• Spiritual
• Lifestyle
• Career/work
	Multidisciplinary Collaborative Care
	• Self-management programs
	• Counselling
	• Physical activity
		Multidisciplinary Collaborative Care
		• Diagnostic procedures
		• Treatment
		• Symptom management
		• Referral/advice addressing late-effects
		  ○ Physical
		  ○ Psychological
		  ○ Social
		  ○ Spiritual

Advocacy • Self & access to services • Others, community	**Advocacy** • Access to services	**Advocacy** • Survivor care services

Fig. 20.5 Pillars of the models of cancer survivorship care: Australia

20.5.4 Asia

Cancer survivorship programs in the Asian countries are not as extensive as the programs in European and North American countries; in fact, cancer survivorship is still in its infancy in Asia [58]. Culture is an important consideration for cancer programs; although experienced in other countries, stigma (that cancer is contagious or a punishment for wrongdoing) continues to play an important role in cancer care and cancer survivorship. In some South Asian countries, negative beliefs persist [59]. It is thought that disclosure of the diagnosis would bring shame to the family,

and such fear reduces the possibility for cancer treatment. Sometimes even victim blaming may occur following a diagnosis, attributable to the costs of care that can become a burden to the family [59].

There has been some progress made to address the needs of cancer survivors in Asia. A recent study of breast cancer survivors assessed their perceptions of barriers posttreatment to examine ethno-cultural differences to enhance the delivery and experience of their care [58]. Women in this study preferred follow-up care in specialized cancer centers rather than seeing a general practitioner or a primary care provider. These providers were perceived as less knowledgeable about their conditions than the specialized center providers. This barrier illustrates an important area of concern as the cancer burden and the demand for care increases in Asia, and in other parts of the world, survivorship care in specialized centers or access to oncology specialists may become limited [60]. Chan et al. (2017) recommends supporting the transition of the patient from the specialized centers to primary care providers through the use of electronic survivorship care plans and the bolstering of cancer survivorship skills in primary care [58]. They also note that a randomized controlled trial is underway to evaluate a multidisciplinary survivorship program that has been culturally adapted for Asian breast cancer survivors.

It is important to note that this lack of confidence in general practitioners over specialized oncology team members is not held by only those in Asia, this has also been found in Italy [61]. Furthermore, a systematic review [60] reported primary care physicians finding barriers in providing cancer to patients because primary-care guidelines were not well defined or consistent for cancer survivors because of training issues and providers' lack of confidence to provide care by stage of cancer care.

China China has a population of about 1.37 billion. China has been reported by the WHO to spend substantially more on healthcare per capita than do India and Indonesia, approximately $731, $299, and $267 per person, respectively (in 2014 US dollars) [62], but less than Japan ($3727) which is relatively less than Germany ($5182), France ($4508), Canada ($4641), or the United States ($9403) [63]. According to the prediction of the IARC, the incidence of cancer in China will increase from 3.1 million in 2012 to 5.5 million in 2035 [64]. Despite this the burden of cancer was unclear until recently. The first systematic analysis exploring the population-based cancer survival involved cases diagnosed in 2003–2005 and followed until the end of 2010; survival for rural cancer patients was almost half that of their urban counterparts for all cancers combined (21.8% vs. 39.5%) [65]. The researchers concluded that the low population survival rates point to an urgent need for government policy changes, including an investment to improve health services for diagnosis and treatment of cancer. Progress has been made in the last decade to advance the Chinese healthcare system, yet the lack of human and other resources in cancer care, large geographical span, diverse cultures, and socioeconomic groups similar to some countries create wide disparities in cancer care within China [17].

Despite disparities and the lack of quality cancer care, there is an urge to accelerate the implementation of cancer survivorship/rehabilitation programs in different provinces in China. There are about 99 cancer rehabilitation organizations in China that are officially recognized by the Chinese Cancer Rehabilitation Society (CCRS) [66]. This society is a nongovernmental organization (NGO) established in 1990. The society aims to provide guidance for cancer patients to receive rehabilitation and create a model for other nonprofit organizations in efforts to implement cancer rehabilitation programs. Currently, the society has connections with 99 cancer organizations in 27 provinces of China. CCRS also collaborates with government institutions such as the Chinese Center for Disease Control and Prevention and overseas nonprofit organizations such as the American Cancer Society involvement in China. Talks, workshops, and seminars are held by health professionals to provide cancer-related information and consultation to the public as a whole and specifically cancer patients to provide

information on medical services particularly during primary treatment. At present, a very small effort is directed at survivorship issues related to health and quality of life post-cancer treatment. Similarly, the Shanghai Cancer Recovery Club (SCRC), an NGO established its own cancer rehabilitation school in 1993.

The cancer rehabilitation school provides a 3-week rehabilitation training program that focuses on cancer recovery education, providing psychological support and assistance with societal reintegration for cancer patients who have completed their hospital treatment [67]. There have been 6500 graduates since its establishment. The essential features of the 3-week rehabilitation training program include support groups that are categorized by different types of cancer, mindfulness meditation, qigong, music therapy, cognitive behavioral therapy, relaxation training, workshops, and talks [68].

The SCRC collaborated with Fudan University School of Public Health in 2016 to examine the effectiveness of the psychosocial intervention component of the 3-week rehabilitation training program using a limited single group design with a pretest-posttest design. Results found that after the 3-week training program there was a significant improvement in the quality of life of the cancer survivors and this improvement persisted 6 months after the program. Moreover, there was an increase in the frequency of physical training by the cancer survivors 6 months after the program when compared to baseline [68].

Clearly, there is more work needed in China to address cancer care and the needs of cancer survivors. While systematic and well-rounded cancer rehabilitation centers have been established in major cities such as Beijing and Shanghai since the late 1980s, the concept of cancer rehabilitation/survivorship programs is still new or even unheard of in remote provinces. The SCRC has provided suggestions for revisions of the national health insurance and policies to expand cancer care and generate more programming for cancer survivorship [68].

Hong Kong Hong Kong has been ranked as one of the healthiest places in the world, yet Hong Kong spends considerably less than the United States on healthcare, with the United States spending nearly 2.5 times what Hong Kong spends [69]. Hong Kong's strong ranking in healthcare is believed to be due to its early health education, professional health services, and well-developed healthcare and medication systems. Moreover, the public healthcare in Hong Kong is virtually free for individuals in a system that leads the world in healthcare with a goal that every citizen in Hong Kong receive lifelong holistic healthcare and that no one is denied adequate medical treatment due to lack of ability to pay for care [69].

Despite these efforts, a recent study found that there is still an unmet need for improved information support and continuity of care for breast cancer survivors [70]. These limitations were also found in another study of women with advanced stage breast cancer where the psychosocial needs of these women were clearly not met by Hong Kong's current medical system [71]. Finally, another study that followed 371 women with breast cancer for 6 months after cancer treatment indicted that nearly half of the survivors had concerns related to residual physical symptoms and a strong need for improved information support and continuity of care problems experienced in other parts of the world as well [70].

Similarly, for childhood cancer survivors, the needs were also not met by the healthcare system. For example, a study that used a structured telephone survey of 614 childhood cancer survivors and 208 sibling controls found that survivors had significantly lower mean scores in physical role and functioning, whereas their mental, social, and psychological well-being was similar to that of their sibling controls [72]. The researchers recommended that childhood cancer survivors could benefit from appropriate screening and counseling at an early stage to mitigate their survivorship difficulties.

Although Hong Kong has a relatively high-quality healthcare system, it is clear that this system could benefit from the inclusion of cancer survivorship programs or other efforts to address the specific needs of cancer survivors. A nongovernmental organization (NGO) established in

1987, the Hong Kong Cancer Fund, aimed at providing cancer support to Hong Kong cancer patients and survivors. "Cancer Link" is a subdivision of the Hong Kong Cancer Fund (http://www.cancer-fund.org), which provides psychosocial support and rehabilitation programs to the cancer patients, survivors, caregivers, and the family members. The support services include nursing consultation, professional counseling, complementary therapies, self-enhancement programs, peer support groups, workshops, presentations, and a hotline. However, the healthcare system as a whole and those surviving diagnosis and treatment could benefit from a cancer survivorship model of care that addresses coordination of care, including screening and recommendations for ongoing care, as well as psychosocial and informational support.

Japan Japan's expenditures on healthcare are relatively low when compared to other developed countries with Japan spending about 8% of its gross domestic product (GDP) on healthcare compared to 11% in Germany, France, or Canada, and 17% in the United States [73]. The Japan Cancer Surveillance Research Group has been involved in cancer monitoring in Japan since the year 2000. The prevalent cancers in Japan are pancreatic, liver, colorectal, and stomach cancer.

Cancer treatment is widely available in Japan. The National Cancer Center Japan, founded in 1962 as a center for cancer treatment and research in Japan, has become a strong leader in the field in cancer treatment but falls short for cancer survivorship care [74]. Some of the limitations in cancer survivorship care may also be related to cultural issues. For example, it is part of the Japanese culture to have a strong reliance on family for the social care needs of individuals rather than an organized social welfare system [73]. Thus, the development and support of a system to address many common challenges of cancer survivorship in Japan is nearly nonexistent. However, family support if better informed might be an avenue to improve cancer survivorship in Japan.

A population-based study in Japan highlighted some of the ongoing issues for cancer survivors in Japan including cancer prevention. Nakamura et al. (2015) found insufficient support for smoking cessation in cancer survivors, reporting that this is in part related to the lack of knowledge in general physicians about cancer survivorship. They also note that at this time there is no prevention of second primary cancers among cancer survivors and pointed to the need to establish specific health management strategies for cancer survivors with a focus on the prevention of noncommunicable disease [75].

In summary, the cancer survival rate is higher in many developed Asian countries or regions such as Singapore, South Korea, and Hong Kong than those developing Asian countries such as China, India, the Philippines, and Thailand. In addition, there is a disparity in the development of traditional medical services and cancer rehabilitation programs between urban and rural areas. How to provide cancer rehabilitation or specific survivorship programs to the rural and less-developed regions is an important consideration for policy makers and the NGOs of the developing Asian countries. The cancer rehabilitation programs in both the developed and developing Asian countries vary widely and remain a work in progress related to comprehensive development and implementation despite the fact that there are a growing number of cancer survivors. Long-term survivorship programs need to be implemented and evaluated as most of the existing cancer rehabilitation programs are only provided for care immediately post-cancer treatment.

20.6 Variations in Priorities of Unmet Needs Across Countries

There is evidence that unmet needs are experienced among cancer survivors across the globe yet there are subtle differences. Addressing the physical, psychological, and emotional needs of cancer survivors across the globe will continue to evolve. Based on limited research, while there are common unmet needs of cancer survivors across countries, the "one-size-fits-all" approach is far from optimal. It is important that we recognize that not all countries have similar priorities of unmet needs and that these needs can vary based on culture specific sensitivities and existing local

healthcare infrastructure. Approaches cannot simply be shared across nations without considering these differences.

Scientific research is needed to examine the long-term effect of various types of cancer survivorship programs to examine how they impact the quality of healthcare received, function, and well-being. How to create a tailored survivorship program that is culturally sensitive to ease social challenges and meet the diverse needs of cancer survivors is a future direction for the both researchers and providers of the cancer survivorship program in countries. It also included many prominent policy makers, researchers, and experts in cancer prevention and control as partners [5]. The International Cancer Information Service Group (ICISG), an affiliate of the UICC, is a worldwide network of more than 70 organizations that provide free and confidential information related to cancer and support services to cancer patients, their family and friends, the public, and healthcare professionals [76]. These global organizations are critical as most of the Third World nations currently do not offer much in the way of support services such as the informal services offered in Jamaica, Latin America, or Thailand.

This cataloguing of programs in various countries is far from complete. What is clear is that much has been accomplished in terms of establishing cancer survivorship programs in many parts of the globe. Although there is some empirical evidence for their effectiveness, organized multidisciplinary research on such programs is necessary in order for us to obtain a better sense of the quality and outcomes of the many programs that evolve. Such efforts have the potential to optimize the outcomes of such programs to meet the needs of the cancer survivors worldwide.

20.7 Summary and Future Directions

Many countries provide varying levels of cancer survivorship care. The challenges post diagnosis and cancer treatment across several countries may vary, though the essential concerns are similar. While different countries will prioritize cancer control in different ways, survivorship care is of global concern, because of a general desire to ensure that people have the best chance of survival, with the best possible quality of life and with minimal consequences from treatment. The use of the Internet has created a forum for information sharing on all levels within cancer treatment and survivorship including support, education, information, and data sharing by international cancer-based organizations. Attending to cultural variation or sensitivities programming of the successful programs can be transported [58, 72, 73]. However, much more international and interdisciplinary collaboration across organizations and research institutions is needed.

The number of cancer survivors is a function of cancer incidence and treatment success. As discussed throughout this text, survivors may experience a broad range of consequences following cancer and its treatments. These consequences may impair quality care, functional outcomes, financial stability, and quality of life and may even contribute to premature death. Numerous studies, albeit predominantly from developed countries, suggest that the care of survivors after initial treatments remains suboptimal [77]. There has been much progress made since the US Institute of Medicine report, specifically pertaining to the first recommendation that “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” [24]. However, there is still a significant variation in awareness of the need to reform survivorship care around the globe [78].

Developing countries are reliant on the more developed world for support and assistance with their cancer burden, particularly through efforts of the WHO and other international organizations. The WHO works with and through the NGOs in nations across the world to provide resources, direction, and support. The Union for International Cancer Control (UICC) works to reduce the global cancer burden and currently

has over 1000 member organizations comprised of some of the world's major cancer societies, ministries of health, and patient groups. It also includes more than 50 prominent policy makers, researchers, and experts in cancer prevention and control as partners [5]. The International Cancer Information Service Group (ICISG), an affiliate of the UICC, is a worldwide network of more than 70 organizations that provide free and confidential information cancer and support services to cancer patients, their family and friends, the public, and healthcare professionals [76]. These global organizations are critical as most of the Third World nations are lacking in basic cancer treatment capacity and thus limit any progress being made to promote cancer survivorship.

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Part VII

Future Directions

21 Lessons Learned and Challenges Ahead

Michael Feuerstein and Larissa Nekhlyudov

21.1 Introduction

Much progress has been made in the field of cancer survivorship since the first edition of this Handbook. Yet, there are many challenges that are still faced by cancer survivors, caregivers, health-care providers, and those leading health-care policy in the United States and in nations around the globe. The chapters in this Handbook summarize much of this progress.

In this chapter, we offer insights into the existing challenges that are relevant for all stakeholder groups to consider. We hope that over the next decade, we will be able to address many of these challenges.

21.2 Clinical Practice

As illustrated by the authors in this Handbook, cancer survivorship has gained recognition as a distinct phase of the cancer continuum. The Institute of Medicine report "Lost in Transition" played a critical role in outlining the challenges in providing quality, comprehensive care for cancer survivors and proposed a path to further empower survivors, educate providers, and develop strategies to improve quality of clinical care. Whereas previously left on their own after a cancer diagnosis and treatment, patients can now more readily get the needed clinical guidance and, to a lesser degree, receive the type of integrated, coordinated follow-up that has the potential to improve their long-term health, function, and well-being. Many clinical sites now offer a variety of specialized clinics and services targeting this patient population. While multispecialty and multidisciplinary clinicians are working together to assist cancer survivors to improve residual symptoms, rehabilitate deficits in function, and improve their sense of well-being, the impact of such models on outcomes and their sustainability in terms of cost and capacity is unknown.

Though slow in uptake, the survivorship care plans are being promoted as vehicles to summarize treatment exposures and subsequent follow-up. Providers now have communication tools that they can use to more proactively assist survivors in improving their health and lives. While a great first step, such tools are meant to inform survivors and their primary care providers regarding the next steps in their care, but data to date suggests that this may be insufficient for achieving long-term health. Follow-through on the part of the survivor and health-care providers is also

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necessary. A number of guidelines, previously offering consensus-based information regarding the management of cancer survivors, are now emerging with evidence-based recommendations. However, it is well known that guidelines are not always adhered to and their impact on many important outcomes or unmet needs remains unknown.

As described in this Handbook, efforts to improve the health and lives of many survivors of cancer are occurring in North America, Europe, Australia, and to a lesser extent throughout the world. Around the globe, interest in cancer survivorship is growing, with the emergence of subgroups within professional organizations (e.g., onco-cardiology, onco-generalism, cancer rehabilitation, psycho-oncology, etc.) and efforts to harmonize international guidelines.

Despite this progress, much more needs to be accomplished especially if we are to meet the demands predicted over the next few decades. The population of cancer survivors is growing, getting older, and often confronts numerous comorbid medical conditions. While there are a number of health-care delivery models that have been proposed, they still need to be systematically evaluated and, if effective, disseminated into clinical practice. Much more needs to be done to assure that patients are still not "lost in transition," do not receive redundant or prolonged ineffective care, or receive no attention. Whether they are transitioned to primary care, continue in shared care models, remain at the cancer center, or are risk-stratified into appropriate health-care settings, follow-up evaluation and care must not be left to chance.

There is still a need for the development and implementation of evidence-based systems or pathways that will allow us to guide the most appropriate care for survivors with different risks and health-care needs. We must ensure that academic cancer centers, community cancer practices, and general medical settings are equipped to care for cancer survivors. We must acknowledge that the reach of the specialized survivorship clinics is limited. We need to be able to assess survivors' risks and be sure that all are cared for, not simply those who have access to such services. Further, as discussed in this Handbook, we must collaborate with our international colleagues in order to learn from one another to enhance the care for survivors worldwide.

There are now evidence-based approaches that help alleviate survivors' distress, fatigue, functional and cognitive impairments, and even problems with interpersonal relationships. Yet, while these exist, assessment of survivors' psychosocial and physical symptoms is not routinely completed, and interventions are often not available or accessible. For example, while cognitive behavioral therapy has been shown effective for depression, insomnia, and other conditions, finding specialists trained in specific techniques is often not possible. Insurance coverage for such services may also not be available, so that the financial cost of these approaches can pose a major barrier to access for many survivors. Likewise, cancer survivors continue to suffer with pain that is not optimally managed, as there are few available holistic, multidisciplinary clinics that offer alternative treatment options and targeted physical therapy.

Whether physicians, nurses, nurse practitioners, or other health-care professionals, we need to educate and train the current and future health-care workforce to provide such services to this ever-increasing population, both in the front line and in specialized care for certain complex cases. As the needed services become available, we can then accelerate the collection of patient-centered outcomes in clinical settings, more readily address patient needs, and monitor their responses to treatment. This feedback loop is critical in order to learn and modify our current approaches. With the digital age clearly upon us, we need to consider online and virtual options to further expand services that can assist us in addressing patient needs, including provision of survivorship care plans, comprehensive monitoring of targeted problems, and even enhanced access to treatment for certain psychosocial symptoms.

Chapters in this Handbook remind us of the importance of healthy lifestyles, including exercise, smoking cessation, and nutrition for

cancer survivors. The authors of these chapters have provided us with a greater understanding of the effect of lifestyle factors in this patient population as well as how we can help survivors to achieve healthier lifestyles. This is clearly of importance to many cancer survivors, yet clinicians continue to struggle with counseling patients about preventive strategies. Published interventions have been successful, but often lacking long-term follow-up. While those in the various fields of cancer survivorship may focus on ways to provide such services to survivors, it may be necessary for health-care systems to be proactive and offer sustainable interventions to all those with chronic medical conditions.

Lastly, we must acknowledge the daily challenges of clinical practice. While the electronic medical records may have enhanced care coordination and communication, there are now more "boxes to click," quality metrics to achieve, and patients to see. Health-care professionals are often not able to keep up. As we ask the clinicians to review their cancer survivors' history, assess their risks, manage their late effects, address their psychosocial concerns, manage their comorbid medical conditions, and counsel them on preventive strategies, we must be cautious that we are not tipping the scales and aiming for the unachievable. It is important to realize that there are other health-care providers who may be available to collaborate with in order to achieve many of the goals stated above. We also must not forget the cancer survivors themselves as playing a potential role as an active member of the care team.

21.3 Research

There has been a tremendous surge in research focusing on cancer survivors, and while we have learned much over the past decade, gaps in knowledge continue to exist and are elaborated on in many chapters in this Handbook. Decades after the introduction of the term "cancer survivor," controversy remains as to what the term means and what are the essential areas of research in cancer survivorship. Many of the authors in this revision struggled with identifying the appropriate phase of follow-up, e.g., after diagnosis, after cancer treatment, which previously included time-limited surgery, chemotherapy and radiotherapy, or even caregivers to focus on. Survivors may now remain in treatment for years, for example, on oral adjuvant therapy or long-term chemotherapy for those with advanced or "chronic" cancer. We suggest that the research community carefully define their population based on the natural history of problems following a specific cancer type and its primary treatment and provide more detailed information on the inclusion criteria, including years since diagnosis, stages, treatment received, and other relevant identifiers. It is through such a standard case definition that study findings will be more meaningfully evaluated, compared, and combined, leading to accelerated scientific knowledge and application at the bedside.

Research must also expand focus on cancer survivor populations that have received less attention over the past decade, specifically those with cancers other than breast, age over 65 years, adolescents and young adults, and underrepresented minority groups. As noted in the prior section, we must be able to offer evidence-based services to diverse cancer survivors in "real-world" clinical settings and promote sustainable long-term outcomes. Further, in some areas that have shown substantial evidence, such as psychosocial and lifestyle interventions, we must now move to dissemination, implementation, and long-term effectiveness.

A challenge in research has been in identifying those cancer survivors who experience cancer recurrence (as this outcome is not readily available in state-based cancer registries) and/or new cancers. While there is evidence that dose of exposures and lifestyle are associated with these outcomes, well-designed epidemiological studies of other suspected risks are needed. As highlighted in the epidemiology chapter, researchers should take advantage of the survivor cohorts and their respective data that have been compiled over the past decade. Much can be learned from the research and translational methodologies applied by those conducting analyses using the

childhood cancer survivor cohorts, leading to important, practice-altering, evidence about long-term effects.

It remains a challenge to demonstrate to payers that there is a benefit of providing cancer survivorship care so that services are both covered (for the patients) and reimbursed (for the provider). In addition to focusing on much needed patient-centered outcomes, research should address how some of these interventions can also affect mortality (as has now been demonstrated in palliative care) as well as quality of life.

Cost of care has always been a concern and will become even more evident as the populations of cancer survivors increase. Defining quality outcomes in cancer survivorship care, including associated costs (patient, provider, and system levels) is needed. Further, while it is clear that the assessment and management of many of the long-term or late effects of cancer treatment have improved over the last decade, the mechanisms for such problems have not been adequately harnessed to be able to prevent or fully manage them. For example, does the identification and active management of cardiovascular risk factors during cancer treatment and following completion reduce the incidence, severity, and mortality of cardiovascular disease? What are the biobehavioral pathways related to improvements in distress or sleep in long-term cancer survivors and what effect do these underlying mechanisms have on various health outcomes?

The past decade has witnessed a revolution in regard to personalized or precision medicine, and in survivorship, there is growing interest in identifying the biological mechanisms for late- and long-term effects of treatment, and finding mitigating factors to reduce such effects. It will be exciting to see how this may shape up in the future of cancer survivorship.

While current research supports the role of increased physical activity or specific types of exercise, initiation of and adherence to these regimens remain a major challenge especially for those who were not active prior to cancer diagnosis and treatment. It is time that new concepts and approaches that more precisely identify factors that can prospectively predict adoption, adherence, and maintenance of many types of health behaviors in cancer survivors emerge. While theories and concepts that are used to help explain initiation and maintenance of various health behaviors have been available for years (many have guided us for decades), there is a need for innovative ways of conceptualizing these health behaviors and how best to initiate and maintain them.

21.4 Policy

Access to health insurance and to health care remains an issue for cancer survivors. While the implementation of the Affordable Care Act (ACA) in the United States likely had beneficial effects on this population, there is limited data to provide evidence in that regard. At this time, the future of the ACA is not clear; policy makers must continue to address the needs of this population in the years to come. It is critical that insurance designs take into account the long-term needs of cancer survivors, including the need for many long-term high-cost services, often leading to financial burden for years following treatment. Health-care payment incentives must also align with the needs of cancer survivors, such that appropriate evidence-based care is promoted and costs are saved by avoiding rendering testing and imaging that has been shown noneffective. As models of care are being tested, it is always important to assess quality and value. Work challenges including the inability to return to work or remain at work across cancer types can trigger major financial burden for cancer survivors and need to be better understood. Policy should focus on facilitating truly effective solutions that involve the cancer team, cancer survivors, and stakeholders from conventional and emerging workplaces.

Across the globe, efforts to improve the care for cancer survivors are variable. Many Scandinavian and Western European countries provide equitable care to all of their citizens, but

others in the developing world may not be accessing quality survivorship care. There must be greater attention on finding ways to reduce disparities, based on race/ethnicity and socioeconomic status in the United States and around the world. Greater emphasis on the older patient should be a priority as well, given the global "graying" and the longer and more functional lives individuals are currently living and are expected do so over the next few decades. Empowering communities, both patients and medical providers, and in particular, the underserved, to improve the quality of care for cancer survivors in their local communities is essential. Political action to enhance health insurance coverage or financial support for underserved populations and countries in order to improve access and costs of care must be seriously promoted across the globe.

21.5 Conclusions

It is rewarding to write this conclusion and take stock of the tremendous strides made in the area of cancer survivorship. There is now an increased understanding of the natural history of cancers and their trajectories, as well as the impact of psychosocial and physical late effects, importance of health promotion, and the challenges of health-care delivery. In the years to come, we hope that health-care professionals continue to learn more about the many health and other challenges cancer survivors confront and strive to provide them with high-quality care; that researchers continue to expand into new directions aiming to understand, prevent, and reduce suffering due to late effects; and that policy makers continue to promote equitable, affordable, and accessible care for all cancer survivors.

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