Michael Feuerstein
Larissa Nekhlyudov *Editors*

Handbook of Cancer Survivorship

Second Edition

Springer

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Journal of Cancer Survivorship:
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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

Reference

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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

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

1

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.

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

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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

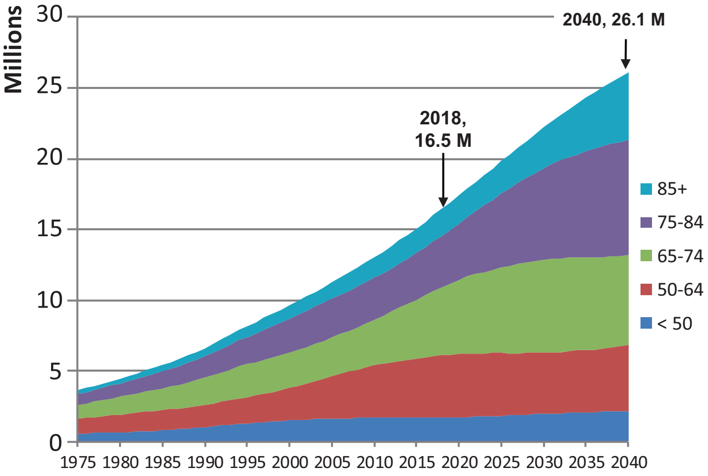

Fig. 2.1 Estimated and projected numbers of US cancer survivors by age at prevalence. Projections after 2013 are based on the US census population projections and flat cancer incidence and survival trends [34]

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

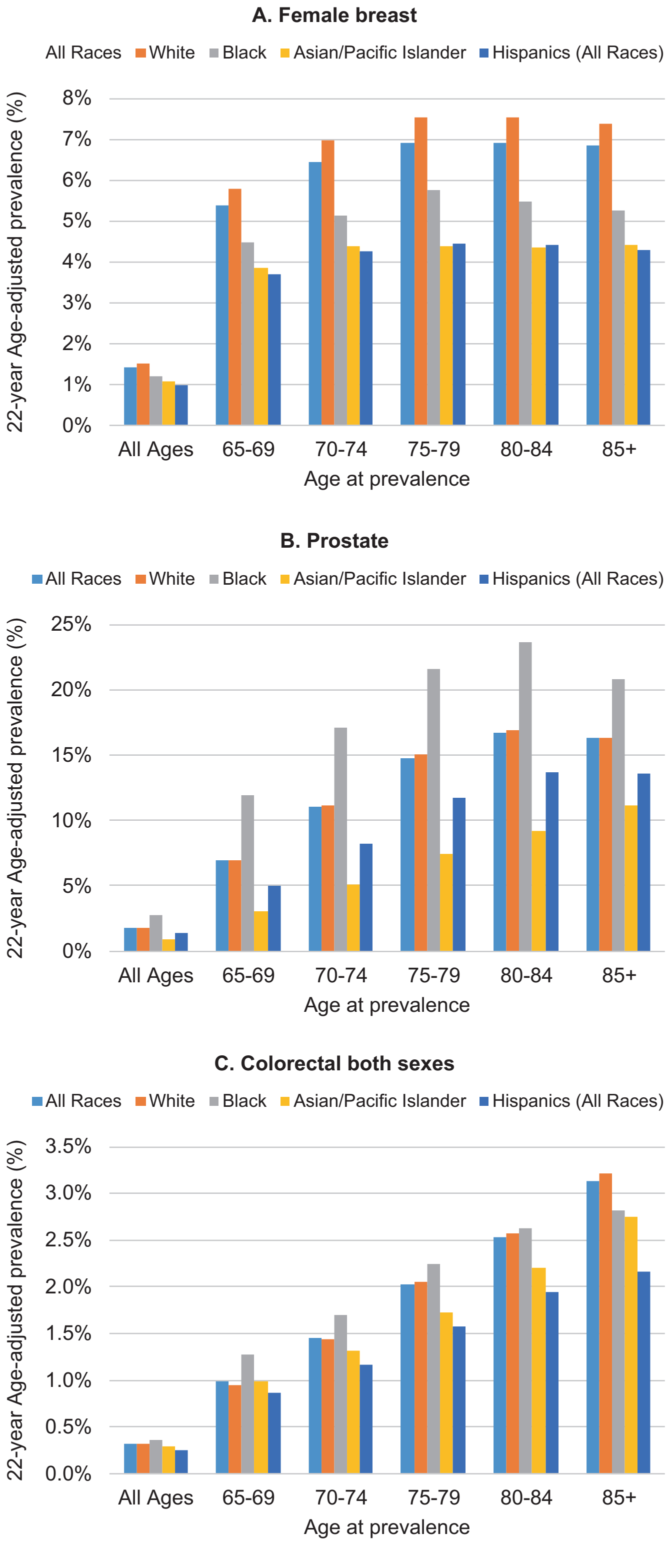

Fig. 2.2 Percent of (A) breast, (B) prostate and (C) colorectal cancer survivors diagnosed between 1/1/1992 and 12/31/2013 among each respective sex/race/ethnicity population by age. The 22-year percent prevalence is calculated at 1/1/2014 and age-adjusted to the US 2000 standard population. The table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

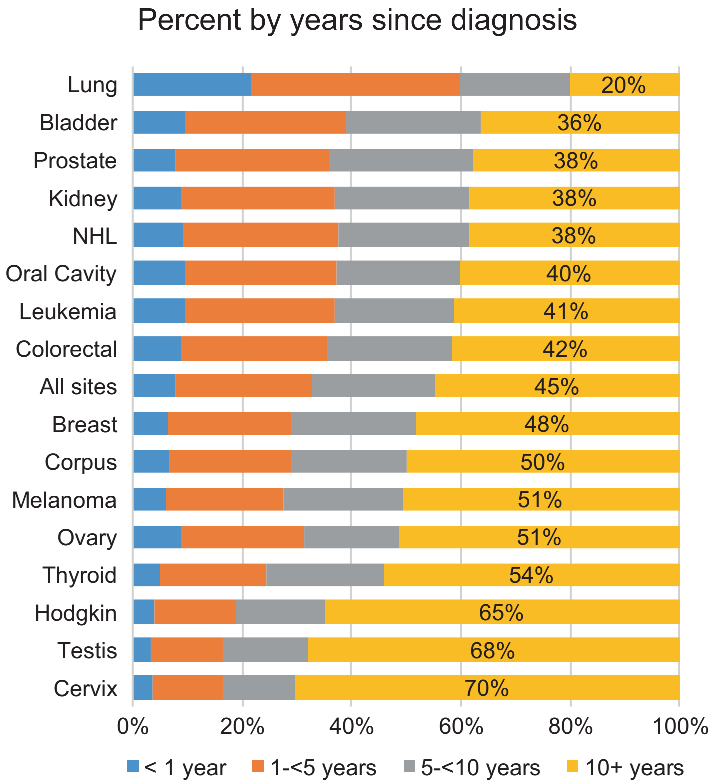

Fig. 2.3 Estimated number of cancer survivors in the United States as of January 1, 2018 by cancer site and years from diagnosis. Cancer sites by ordered proportion of survivors 10+ years from diagnosis. Median age at diagnosis for patients diagnosed in 2010–2014 and 5-year relative survival for patients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