Supportive Cancer Care

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Editors

Springer

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We the editors of this first edition of Supportive Cancer Care wish to thank each chapter author for their outstanding contributions and especially great patience with the considerable complexity of putting together a coordinated textbook with many different themes and moving parts.

We are inspired by our amazing cancer patients, who battle every day of their lives to survive and have quality time with their family and friends. We only exist professionally to help our patients become long-term cancer survivors with a high quality of life.

In 2005, Dr. Karen Weihs and l conceived a plan, aided strategically by Dr. Thomas Brown, to provide a comprehensive supportive cancer care program in the University of Arizona Cancer Center with five essential elements to be incorporated into our new Peter and Paula Fasseas Cancer Clinic, opened in 2007. These five elements include the following: (1) psychosocial oncology, (2) cancer survivorship planning, (3) palliative care, (4) integrative medicine touch therapies, and (5) high risk genetic counseling.

Of course, this ambitious supportive cancer care program requires strong integration and a continuous search for funding from our healthcare system (Banner University Medicine) and our dedicated donors. We would like to give a special thank you to Mel Zuckerman and Family, founder and first CEO of The Canyon Ranch, and to Nance Crosby and her Hope Has a Name Fund for their generous contributions to our integrative touch therapies clinics. The development of this supportive cancer care program served as the inspiration for the present Supportive Cancer Care textbook.

We have personal dedications as follows:

David S. Alberts, M.D: I would like to dedicate this book for Heather, my magnificent "Better Than Ever" mate of more than 55 years, to know that she has been the continuous inspiration for everything I have accomplished over 50 years as a physician, scientist, and rational, loving being.

Maria Lluria-Prevatt, Ph.D: I would like to dedicate my efforts of this book to Dr. David Alberts who constantly inspires me with his countless years of service to all cancer patients, seeking to provide them the very best treatment and support as well as his lifelong pursuit of cancer prevention methods that will give the future generations a cancer-free life. I also dedicate this to my mother and father, Ligia and Mario Lluria, who always inspire me with their tremendous intelligence, dedication, and faith. Also to my husband, Jeff, and finally, to my three amazing children Matthew, Sofia, and Angela who brought me tea and chocolate when

editing deadlines emerged and who have learned so much in the importance of preventing and curing cancer. I would also like to acknowledge Isabel Gossler, a rising young star in the field of medicine, for her significant contributions in the final editing of this book.

Stephanie T. Kha, B.S.: I would like to dedicate my contributions of this textbook to my wonderful supportive parents, Nam and Shirley Kha, who have always inspired me to strive for excellence in my studies, my hobbies, and my passions.

Karen L. Weihs: I would like my dedication to include appreciation for the inspiration and encouraging support I receive from my life partner, Richard D. Lane, MD, Ph.D., and of course, the patients whose determination and creativity in the face of cancer teach me something new each day.

Contents

Introduction

1

David Alberts, Maria Lluria-Prevatt, Stephanie Kha, and Karen Weihs

The cancer experience exists as a continuum, beginning with diagnosis and continuing through the phases of treatment toward long-term survival [1]. The term "cancer survivor" is used to describe any person diagnosed with cancer, including those currently fighting the disease or those who have become cancer-free. Treatments aim to remove all traces of the cancer from the body, prolong survival, and provide the highest possible quality of life. However, many survivors experience adverse long-term effects from the treatment, including physical and/or psychological symptoms. Supportive cancer care is designed to understand and treat these cancer-associated and cancer-induced symptoms to provide lasting physical and emotional well-being for survivors and their families at all stages of the illness [2]. Education, management, and continuous support are essential to reducing these adverse side effects of cancer and its treatments in order to enhance the quality of life for cancer patients and caregivers.

The goal of this book, *Supportive Cancer Care*, is to provide a thorough and critical understanding of the supportive care issues that affect cancer survivorship. It is of great importance that patients and caregivers are both actively involved in the decision-making process with healthcare providers regarding treatment, symptom management, and long-term survivorship plans. Having the information and access

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to supportive care resources can improve the cancer survivorship experience and facilitate these decisions that affect the quality of life for survivors and caregivers, on both a national and international scale.

Cancer is a leading cause of disease, with an estimated 14.1 million new cancer cases occurring worldwide in 2012, according to the International Agency for Research on Cancer (IARC) [3]. Cancer is also a leading cause of death globally, with an estimated 8.2 million deaths in 2012 [3]. There were 32.6 million people alive worldwide at the end of 2012 with a cancer diagnosis in the previous 5 years, and the three most commonly diagnosed cancers were lung (13 %), breast (11.9 %), and colorectal cancers (9.7 %) [3, 4]. Predictions by GLOBOCAN 2012 calculate the new number of cancer cases per year to increase to 19.3 million in 2025 [3].

This trend of an increasing population of cancer survivors has been studied extensively in the United States. On January 1, 2014, nearly 14.5 million people were living with a history of cancer in the United States, and this number is predicted to reach 19 million by January 1, 2024 [5]. This estimate is calculated based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database and does not include basal cell or squamous cell skin cancers or carcinomas in situ of any site except the urinary bladder. The increase in the number of cancer survivors is attributed to the early detection and improved treatment for this disease in combination with an aging and growing population [5]. Of the total cancer survivors in the United States, 46 % are aged 70 years or older, whereas only 5 % are aged 40 years or younger. More than half of the cancer survivors (64 %) in the United States were diagnosed five or more years ago, and 15 % were diagnosed with cancer 20 or more years ago. Among males, the three most prevalent types of cancers are prostate cancer (43 %), colorectal cancer (9 %), and melanoma (8 %); among females, the three most prevalent cancers are breast cancer (41 %), uterine cancer (8 %), and colorectal cancer (8 %) [5]. The prevalence of cancer and its specific disease sites demonstrate the importance of understanding the unique characteristics and needs of each patient to provide supportive care resources throughout the many phases of cancer survivorship. The role of *patient navigation* throughout these phases of survivorship and the complexities of cancer care is the first topic explored in the next chapter, with special emphasis on the evolution of the patient navigation concept and its future potential as an organized and established discipline in the context of supportive cancer care.

An important factor to consider in the survival of cancer patients is comorbidity, a condition of having two or more diseases at the same time [6]. Observational studies suggest that cancer patients with comorbidities have poorer survival than patients without comorbidities [6]. When cancer patients have other medical conditions in addition to cancer, the healthcare provider must incorporate comorbidity measurements into the decision-making process to better quantify risk, predict outcomes, and identify treatment options for the patient. Research also suggests that comorbidity can have a considerable impact on cancer detection, stage at diagnosis, choice of treatment, and completion of treatment regimen [6].

According to the National Cancer Institute's December 2013 *Annual Report to the Nation on the Status of Cancer*, the prevalence of comorbidities among the top four cancers (occurring in over half of patients aged 66 years or older) was 52.9 % for lung cancer, 40.7 % for colorectal cancer, 32.2 % for breast cancer, and 30.5 % for prostate cancer [7]. Based on Medicare claims reports, the fifteen new comorbidities identified in patients in the year prior to cancer diagnosis included acute myocardial infarction (heart attack), acquired immunodeficiency syndrome (AIDS), cerebrovascular disease (stroke), chronic renal failure (chronic kidney disease), cirrhosis/chronic hepatitis, congestive heart failure, chronic obstructive pulmonary disease (COPD, lung disease), dementia, diabetes, history of myocardial infarction (irreversible heart disease), liver disease, paralysis, rheumatologic disease (arthritis), ulcer disease, and vascular disease [7]. The most prevalent types of comorbidities among cancer patients were diabetes (16 %), COPD (15.5 %), congestive heart failure (9.7 %), and cerebrovascular disease (6 %) [7]. Depending on the level of severity (low, moderate, or severe) of the comorbidity condition, the cancer treatment may require modification to extend survival and/or maintain quality of life. The level of severity is calculated using scores from claims data and statistical models in the SEER-Medicare linked database [7].

Many different types of treatment have been researched and developed to eliminate cancer and/or ensure the highest possible level of physical and emotional well-being for the patient. When selecting a treatment and developing a treatment plan, it is most important to first discuss and identify the needs and the priorities of the patients and their families. Treatment options can involve surgery, radiation, therapy (chemotherapy, immunotherapy, targeted therapy), and bone marrow transplantation. Palliative and psychosocial care should also be incorporated into the active treatment plan to help minimize pain, symptoms, and stress for patients. From the moment of diagnosis, physical and emotional symptoms begin to negatively affect patients; therefore, it is crucial that discussions on supportive and palliative care occur as early as possible in the course of disease. In 2007, a study of 51 ambulatory patients with advanced non-small cell lung cancer (NSCLC) demonstrated the feasibility of integrating early palliative care with oncology care [8]; in 2012, a study of 151 patients with metastatic NSCLC demonstrated that early palliative care optimized the timing of chemotherapy treatment and hospice care transitions [9], lending support to the positive impact of the services provided by a palliative care team. Chapter 5 of this book examines *Palliative Care* as an essential part of quality care in cancer survivorship.

Unfortunately, there are many common side effects associated with cancer treatment, and these side effects can vary from being acute and short lived to being chronic and persistent. Even after treatment has ended, late effects can arise months or years later, thus affecting both short-term and long-term quality of life. For example, chemotherapy drugs such as vincristine, taxanes, and platinum-based drugs can damage sensory nerve cells and induce weakness, numbness, and pain in the hands and feet of the patient [10]; this condition is termed peripheral neuropathy, and it requires ongoing medical attention because the extent of the damage is dose dependent and may take months or years, if ever, to resolve. Chapters 7 and 8 of this book

explore the *Fundamentals of Pain Management* as well as the *Management of Breakthrough Pain*, respectively.

The management of the physical and psychological symptoms related to cancer and its treatment is crucial for maintaining quality cancer care and meeting the needs of cancer survivors and families. The eleven most common side effects of cancer and its treatment are bone density loss (osteoporosis and osteopenia), cardiotoxicity (heart damage), cognitive (mental) deficits, emotional distress, fatigue, fear of cancer recurrence, infertility, lymphedema, pain, pulmonary (lung) dysfunction, and sexual dysfunction [11]. Coordination of supportive care for physical and psychological side effects is a key aspect in developing a treatment plan. This book features many chapters on the management of specific adverse effects of cancer and its treatment. Chapter 3 delves into *Psychosocial Oncology* as an interdisciplinary specialty of understanding and treating the complex emotional stress and psychological issues associated with the cancer experience. Chapter 4 focuses on the *Management of Depression*, Chaps. 9 and 10 explore *Delayed Nausea/Emesis* and *Fatigue* respectively, and Chap. 11 investigates *Cognitive Function in the Cancer Survivor*. In regard to lifestyle management, Chap. 13 builds upon the foundation of patient-centered care to address *Nutrition and the Cancer Survivor*, and Chap. 14 focuses on the current research and future directions for the symptom management of *Weight Gain*.

In addition to the continuous surveillance for side effects of cancer and its treatment, cancer survivorship plans must also include long-term surveillance for a recurrence of the original cancer or the development of a second primary (new) cancer. Even though treatment of the original cancer may appear to be effective, cancer cells may still persist and grow in the body near to or distant from the site of the original cancer. Cancer survivors have an overall 15 % increased lifetime risk of developing a second primary cancer [12, 13], and this risk may be higher or lower depending on the type of the first cancer diagnosed, the treatment received, and the age at the time of diagnosis [13]. Familial cancer syndromes, genetic susceptibility factors, and carcinogenic exposure also contribute to the risk of developing a subsequent cancer, which is calculated as a ratio of the observed to expected (O/E) number of cancer cases [12, 13]. Survivors with higher O/E ratios, and thus a higher risk for developing a second cancer, include adult survivors of Hodgkin's lymphoma and tobacco use-related cancers, as well as childhood survivors of retinoblastoma, Ewing sarcoma, and Hodgkin's lymphoma [12, 13].

With a continually increasing number of cancer survivors and an abundance of debilitating side effects arising from cancer and its treatment, the need and the demand for cancer survivorship care are urgent and expanding. Many models of survivorship care planning have been developed to address this need of improving the quality of care provided to cancer survivors, and these models are presented and evaluated in Chap. 6 of this book – *Cancer Survivorship Planning*. An important aspect to proper survivorship care in these models is an accurate assessment of a survivor's needs and concerns on a routine basis. Communication and education between patients and physicians, as well as among healthcare providers, are therefore critical to delivering optimal individualized survivorship care.

In 2006, the Institute of Medicine (IOM) began recommending the use of a survivorship treatment summary and care plan individualized to each cancer patient [14]. This comprehensive treatment summary contains personalized, detailed information on the cancer diagnosis (type, stage, date), specific treatments (procedure names, dates, drug names and dosages, radiation dosages, etc.), complications (side effects, hospitalizations, etc.), and supplemental therapy (physical therapy, adjuvant therapy, etc.) [15]. The IOM survivorship care plan includes a schedule of follow-up medical visits (tests, screenings, etc.), a list of symptoms for signs of cancer recurrence, potential long-term treatment effects and symptoms, behavioral recommendations for a healthy recovery, and available community resources [15].

In 2013 and 2014, the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) began releasing evidence-based recommendations to assess and manage the adverse effects of cancer treatment during and after the survivor's active phase of treatment [15, 16]. NCCN's guidelines focus on eight distinct areas: anxiety and depression, cognitive function, exercise, fatigue, immunizations and infections, pain, sexual function, and sleep disorders [17]. ASCO's guidelines focus on the prevention and management of three areas: neuropathy, fatigue, and depression and anxiety [16]. The IOM, ASCO, and NCCN are currently working to establish formal guidelines for physicians on creating survivorship plans for their patients as well as expanding their current recommendations to include the continuing and late effects of various cancer treatments [15–17].

Cancer not only presents a tremendous physical and emotional impact on survivors and their families but it also carries a substantial financial burden to those affected. In the United States, the National Institutes of Health (NIH) estimated the total cost of cancer for the year 2009 to be $216.6 billion, based on Medical Expenditure Panel Survey (MEPS) of the Agency for Healthcare Research and Quality [18]. This total cost is further divided into $86.6 billion as direct costs and $130 billion as indirect costs [18]. The direct costs of cancer involve the payments for the resources (equipment, drugs, therapies, etc.) involved with treatment and rehabilitation. Additionally, the indirect costs include morbidity (loss of income due to days missed from work) and mortality (premature death) costs [19]. Even with private or government health insurance, cancer survivors experience a significant economic burden. In a 2008–2010 healthcare cost analysis, the average annual healthcare expenses for newly diagnosed cancer patients (aged 65 and younger) were $21,222, with $1,463 paid directly by the survivors as an out-of-pocket expense [19]. For individuals with no history of cancer, the annual healthcare expenses averaged at $3450, with $590 in out-of-pocket expenses [19].

Furthermore, there are the hidden costs of cancer that include health insurance premiums and nonmedical expenses such as transportation to and from treatment facility, child or elder care, housekeeping assistance, wigs, and temporary housing accommodation [20]. The financial perspective is thus crucial to understanding the concerns of cost and access among cancer survivors. Chapter 18 – *Health Economic and Outcomes Research in Cancer* – offers valuable insight into the economic impact and efficacy of cancer care resources through a comprehensive and robust analysis of

the current cancer healthcare system. The issue of supportive housing and accommodation for patients and their caregivers during the active phase of treatment is examined in Chap. 18 of this book – *Hospitality Houses for Cancer Patients*.

The integration of supportive and palliative care into the survivor's treatment plan can relieve part of this financial burden by opening communication lines between patients and providers, involving the patient and family as active participants in treatment decisions, and matching the treatment plan to the priorities and desired goals of the patient. Research studies on the cost effectiveness of palliative care interventions showed a significant cost savings among women with platinum-resistant ovarian cancer [21] as well as a significant reduction in hospital length of stay among critical care patients with stage IV malignancy [22].

Reducing cost barriers through care interventions, such as the integration of palliative and supportive resources, is essential because the substantial economic impact of cancer can also affect the survivor's access to treatment and quality care throughout the phases of survivorship. Cancer disparities in treatment and outcomes exist in medically underserved populations, including racial and ethnic minority groups, the uninsured or underinsured, the elderly, and those from rural communities [23, 24].

In the continuum of cancer survivorship, the transition from active treatment to posttreatment care and beyond may benefit greatly from the incorporation of supportive care information and resources into the treatment plan. The concept of the quality of life for survivors involves the physical, emotional, social, and spiritual well-being [25]. Supportive care is designed to address and enhance each of these components using evidence-based recommendations while bearing in mind that each survivor has unique needs and priorities. It is our hope that this book on *Supportive Cancer Care* will bring to light the many existing issues and concerns of cancer survivorship and address the ways in which to improve and ultimately resolve the problematic areas in order to enhance the quality of life for cancer survivors and their families. Despite the recent progress on the increased awareness and research toward supportive care in cancer survivorship, there is still an extensive need for further studies to establish and validate evidence-based guidelines on survivorship care. With an increasing population of cancer survivors, future research toward understanding, preventing, managing, and relieving the physical and psychological adverse effects of cancer and its treatment has the potential to make a truly meaningful impact on millions of cancer survivors and their families.

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Patient Navigation and Supportive Cancer Care

2

Pamela J. Haylock

2.1 Navigation as a Supportive Cancer Care Intervention

In a sense, the essence of patient navigation is support. Concepts of psychological, emotional, social, and spiritual human needs and strategies used to satisfy needs and adapt to demands and changes have been described by Maslow [1]. The concept of need is equated to necessity, an essential condition, not simply a deficiency [2]. In the event of extreme life events, such as the diagnosis of cancer, tasks associated with meeting personal needs may require skills that exceed an individual's capabilities, in which case help and support from another person is necessary to satisfy unmet needs [2]. Hébert and Fillion [2, 3] reason the concept of need is the basis of patient-centered care and suggest that navigators not only detect needs but also devise and implement strategies to satisfy those needs.

Patient navigation entered the health-care lexicon in the 1990s as a community-based strategy to satisfy health-related needs, reduce health disparities among underserved populations, and eliminate gaps and barriers in cancer care [4–6]. Other driving forces for the emergence of navigation as a mechanism to ensure equitable and efficient access to quality cancer care services include [7]:

- Growing understanding of "the cancer journey" and insertion of its place in the policy agenda [8]
- Aging US population and subsequent high cancer burden in this population
- Evolution and acceptance of patients as consumers
- Increasing cultural awareness of health and cancer
- Advances in medical science and technology

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- Internet and consumers' access to health information
- Increasing use of complementary and alternative medicine

By 2010, patient navigation was widely viewed as a strategy to reduce systematic program inefficiencies [9]. In 2015, cancer programs accredited by the American College of Surgeons Commission on Cancer must have patient navigation processes in place [10]. This chapter provides an overview of the evolution, current status, and challenges of patient navigation as a supportive care process and service component of quality cancer care.

2.2 Context of Navigation and the Navigator Role

The emergence of the concept of navigation is linked to the history of cancer and cancer treatment, ever-increasing complexities of cancer care, recognized disparities in cancer-related outcomes, lack of care coordination, and fragmentation of health-care delivery [8].

Patient navigation services emerged as a response to and remedy for disparities in outcomes of cancer care [11]. There is as yet no generally accepted definition of patient navigation or patient navigators, although organizations, health-care delivery systems, and navigation programs do attempt to capture the concept. C-Change [12] and the Oncology Nursing Society (ONS) [13] define patient navigation as a process and/or a service that provides "individual assistance offered to patients, families, and caregivers to help overcome healthcare system barriers and facilitate timely access to quality healthcare." The National Cancer Institute/American Cancer Society-sponsored Patient Navigation Research Program (PNRP) defines patient navigation as

> …support and guidance offered to vulnerable persons with abnormal cancer screening or a new cancer diagnosis, in accessing the cancer care system, overcoming barriers, and facilitating timely, quality care provided in a culturally sensitive manner. [14]

The Patient Navigation Research Program established under the Health Resources and Services Administration asserts patient navigation is intended to target individuals or populations at risk for delays in care and specific time points in the cancer care continuum. Navigation is operationalized as starting at the time of abnormal screening findings and ending when the screening test is determined to be falsely positive or continues through completion of treatment [14].

Nurses, social workers, and lay community peers fill volunteer and employed navigator roles. Sources of funding, roles, titles, job descriptions, tasks, educational and experiential preparation, and credential qualifications were initially disparate and remain so today. As acknowledged in the Association of Community Cancer Centers' (ACCC) Cancer Program Guidelines [15], navigation programs are developed by individual cancer programs or in partnership with a community agency that "understands its unique patient population and its community" suggesting

"individual programs or health systems can best create a navigator system that suits its needs" [15]. While allowing flexibility in navigation program development and implementation, this rationale dismisses the significance of variation in definition, nomenclature, end points and outcomes, style, and scope of patient navigation services and navigators, perpetuating problems in the evaluation of the complex innovation that is patient navigation [11, 14].

2.2.1 Fragmentation and Complexity of Cancer Care

Consider the fact that by the time a person with a new cancer diagnosis begins treatment, he or she has already been assessed by at least five physicians: most likely a primary care provider, surgeon, radiologist, pathologist, medical oncologist, and radiation oncologist. Additional specialist providers are added to the mix as distinct, comprehensive assessments and considerations are needed for infants, children, and adolescents for whom cancer diagnoses complicate developmental phenomena. Additional consultation is equally important for adult patients with comorbid and chronic conditions and/or older persons who have age-related declines in physiologic functions. As treatment or disease progresses, symptom management, psychosocial care, and recovery expertise are often essential components of care. Providers may or may not work in the same health-care system, or they are located in the various buildings, cities, and states, – factors that contribute to lapses in communications and fragmented care. Patients encounter numerous barriers to accessing cancer-related services, particularly patients and families in poor and underserved communities, and, as a result, have inferior morbidity and mortality outcomes [6, 17].

2.2.2 Coordination of Care

The Patient Protection and Affordable Care Act proposes care coordination as a means to improve health-care quality and cost controls [18]. The American Nurses Association (ANA) maintains that the lack of care coordination relates to high costs, uneven quality of care, and unacceptable risks of error, resulting in increased costs in resources, human suffering, and other suboptimal outcomes [19]. In its white paper, *The Value of Nursing Care Coordination,* the ANA defines care coordination in two parts:

> a) …a function that helps ensure that the patient's needs and preferences are met over time with respect to health services and information sharing across people, functions, and sites; and b) the deliberate organization of patient care activities between two or more participants (including the patient) involved in a patient's care to facilitate the appropriate delivery of health care services [19].

Care coordination is an acknowledged component of navigation processes and a core competency of nurses in navigation roles [20, 21].

2.3 Navigation: A Brief History

The term *navigation* is derived from the Middle French (*navigation*) and Latin (*navigationem*) circa 1530 to mean "a sailing, navigation, voyage," – a noun of action from the past participle stem of *navigare* meaning "to sail, sail over, go by sea, steer a ship," from *navis* meaning "ship" plus the root *agere* meaning "to drive" [22]. Until the late 1980s, navigation referred to a field of study focusing on the process of monitoring and controlling the movement of a craft or vehicle from one place to another, also designating the specialized knowledge used by navigators to perform navigation tasks [22].

In the context of health-care delivery, another definition of "navigation" emerged – as nurses, social workers, and lay health-care workers filled navigation roles. Historically, patient navigation emerged in lightning speed. Harold Freeman's leadership, compassion for underserved populations, and tenacity behind the innovative patient navigation program launched in 1990 at New York's Harlem Hospital Center are near legendary and retold in numerous navigation-related resources and stories [23, 24]. Early navigation programs were largely based on Freeman's model, featuring community health workers and patient trust-based peer-to-peer relationships, improved access to care and outcomes in underserved communities [6, 25]. Pioneering efforts in community-based navigation programs focused on reducing disparities in underserved populations by addressing known barriers to diagnostic and treatment services – including disadvantaged socioeconomic status, indifference of systems and providers to cultural and ethnic mores, lack of child care and transportation, and limited health insurance – all documented sources of delayed access to diagnostic and treatment services that result in disparities in cancer outcomes [4, 6, 17, 26].

In 2005, funding support for patient navigation research was created when President George W. Bush signed the Patient Navigator Outreach and Chronic Disease Prevention Act to establish the US Health Resources and Service Administration's (HRSA) Patient Navigation Research Program (PNRP) [27]. Eight research institutions were awarded $25 million in 5-year grants to develop the PNRP for minority and underserved cancer patients [28]. Language in the Patient Protection and Affordable Care Act (ACA) of 2010 supports navigation and navigators [18]. Under ACA provisions, state health exchanges established navigator programs to help American citizens make informed decisions about health insurance enrollment. The ACA extended the Patient Navigator Outreach and Chronic Disease Prevention Act of 2005 grant program from its initially designated conclusion in 2010 to 2015 [18]. The Patient Navigation Assistance Act, introduced to Congress in March 2014, would provide Medicaid coverage for patient navigator services [29]. In 2012, the American College of Surgeons Commission on Cancer (CoC) introduced Standard 3.1, mandating the establishment of community needs-based navigation processes in CoC-accredited cancer programs starting in 2015 [10]. Today, it is widely acknowledged that the US health-care system presents barriers beyond those encountered primarily by underserved and/or racial/ethnic minorities. Hence, navigation is an increasingly expected service available to people served in many – if not most – cancer care settings in the United States.

2.4 Navigation Defined

Although there is no consensus-based definition of navigation, various organizations have working definitions. With minor modification from the original definition crafted by C-Change [12], the joint position on the *Role of Oncology Nursing and Oncology Social Work in Patient Navigation*, the Oncology Nursing Society (ONS), the Association of Oncology Social Work (AOSW), and the National Association of Social Workers (NASW) define patient navigation in the cancer care setting [13]:

> …individualized assistance offered to patients, families, and caregivers to help overcome healthcare system barriers and facilitate timely access to quality health and psychosocial care from pre-diagnosis through all phases of the cancer experience.

Patient navigation programs, according to the Association of Community Cancer Centers' (ACCC) Cancer Program Guidelines, focus on barriers to access without identifying a particular population:

> A patient navigation program is available for patients, their families, and caregivers to help overcome health care system barriers and facilitate timely access to quality medical and psychosocial care from pre-diagnosis through all phases of the cancer experience [15].

The National Coalition of Oncology Nurse Navigators' definitions of oncology nurse navigator and patient navigator differentiate lay and professional roles [30]:

> *Oncology Nurse Navigator* (ONN) —Oncology Nurse Navigator is a professional whose clinical nursing expertise guides patients, families and caregivers to informed decision-making, and who collaborates with a multi-disciplinary team to allow for timely cancer screening, diagnosis, treatment, and increased supportive care across the cancer continuum.
>
> *Patient Navigator* (PN) — The Patient Navigator can be a layperson, a social worker or a nurse who is dedicated to providing individualized assistance to patients, families, and caregivers to help overcome health care system barriers and facilitate timely access to quality medical and psychosocial care from pre-diagnosis through all phases of the cancer experience

2.5 Navigation Described: What Do Navigators Do?

The goal of patient navigation according to the PNRP is "to facilitate timely access to quality cancer care that meets cultural needs and standards of care for all patients" [27]. Freund et al. [27] suggest the concept of patient navigation is based on a care or case management model consisting of four components: (1) a systematic approach to case identification, (2) identification of individual barriers to recommended care, (3) development of an individualized plan to address identified barriers, and (4) a systematic method of tracking each case through problem resolution.

As the PNRP grant program was authorized, outcomes, roles, and tasks of patient navigation were described using language from Section 340A(l)(3) of the Public Health Service Act: "…to provide patient navigator services to reduce barriers and improve health care outcomes, and for other purposes" [31]. Qualified grant applicants were to hire and train patient navigators who have direct knowledge of the communities they serve to facilitate the care of individuals and perform the following duties:

1. Acting as contacts, including by assisting in the coordination of health care services and provider referrals, for individuals who are seeking prevention or early detection services for, or who following a screening or early detection service are found to have a symptom, abnormal finding, or diagnosis of, cancer or other chronic disease.
2. Facilitating the involvement of community organizations in assisting individuals who are at risk for or who have cancer or other chronic diseases to receive better access to high-quality health care services (such as by creating partnerships with patient advocacy groups, charities, health care centers, community hospice centers, other health care providers, or other organizations in the targeted community).
3. Notifying individuals of clinical trials and, on request, facilitating enrollment of eligible individuals in these trials.
4. Anticipating, identifying, and helping patients to overcome barriers within the health care system to ensure prompt diagnostic and treatment resolution of an abnormal finding of cancer or other chronic disease.
5. Coordinating with the relevant health insurance ombudsman programs to provide information to individuals who are at risk for or who have cancer or other chronic diseases about health coverage, including private insurance, health care savings accounts, and other publicly funded programs (such as Medicare, Medicaid, health programs operated by the Department of Veterans Affairs or the Department of Defense, the State Children's Health Insurance Program, and any private or governmental prescription assistance programs).
6. Conducting ongoing outreach to health disparity populations, including the uninsured, rural populations, and other medically underserved populations, in addition to assisting other individuals who are at risk for or who have cancer or other chronic diseases to seek preventative care.

In efforts to describe the responsibilities of patient navigators, Parker et al. acknowledge "service-focused" and "barrier-focused" navigation [11] and caution that either definition could exclude important navigator functions. They framed navigators' work within and external to health-care organizations to "facilitate patients' receipt of care from providers" [11], noting that navigators involve others in their work and navigators' networks of relationships are essential to achieving their objectives. Based on these assumptions, Parker et al. define navigation in terms of tasks and networks: "navigators do things for patients by working with patients and other actors in both the social network of the organization itself and the community in which the organization resides" [11]. The scope of navigation then is a blend of social and professional networks and navigators' activities [11]. The task analysis approach suggested by these researchers not only describes what navigators do but also emphasizes interactions of persons and environment, identifies goals of a task, delineates the criteria to reaching those goals, and acknowledges relevant resources and constraints.

The approach Parker et al. [11] devised was informed by grounded theory methodology, resulting in a set of categories used to sort navigator behaviors [31, 32]. Data were collected at three PNRP sites, offering several contexts from

which to observe navigators. Contextual variations, including the scope of the navigation program, phase of cancer care addressed, emphases on navigator responsibilities, background of navigators, and physical and organizational

Table 2.1 Domains and categories of navigator behaviors (Parker et al. [11])

Tasks Identification and mitigation of barriers with patients		Networks Interactions with a specific patient and/or with providers within and outside immediate location	
Navigating tasks	Examples	Network categories	Examples
Telling	Explaining and describing	Specific patient	Discuss with patient upcoming diagnostic procedure
Inquiring	Assessing for barriers	Providers	Interaction with physician(s) to confirm test results
Supporting	Listening to fears	Nonclinical staff	Interactions with receptionists, administrators, insurers
Coaching	Discussing and helping to frame questions	Supportive services	Interactions with formal (social work, translation, transport staff) and informal (family, friends) groups of supportive care providers
Facilitating tasks	Tasks performed for a specific patient	Paper and/or electronic medical record systems	A means of communication with members of other network categories Requires attention and constant update and consultation
Finding	Case finding; assuring patient's adherence with schedule	Tasks associated with individual patients also translate to establishment of delivery-system-wide and systematic program development to assure consistent navigation-related processes	
Coordinating team communication	Assure all team members' awareness of next steps		
Integrating information	Ensure all types of patient data are documented and shared as needed		
Seek collaboration	Enlist other providers to assist in addressing patient's needs		
Maintain systems' tasks to support all patients	Requires ongoing periodic re-assessment of community and consumer needs, re-evaluation of programmatic priorities, and services available to meet determined priority needs		

(continued)

Table 2.1 (continued)

Tasks Identification and mitigation of barriers with patients		Networks Interactions with a specific patient and/or with providers within and outside immediate location	
Navigating tasks	Examples	Network categories	Examples
Identify potential patients	Review lab, imaging findings to note patients who need follow-up		
Build networks and referral routines	Meet clinicians to explain navigator role and clarify referral criteria and process		
Review cases	Review open issues		
Document activities and review information	Record navigator actions Handling test results: retrieve and enter patient data Process and record other information relevant to navigator role		
Other activities	Activities unrelated to navigation Research Consenting patients Clinical backup Interpreting for non-navigated patients Informal conversations with coworkers		

locations, were noted to influence what navigators do. Guided by *task* and *network* concepts, the authors defined four categories, each for tasks and networks, depicted in Table 2.1.

Job function activities of oncology nurse navigators were also explored in the Oncology Nursing Society's Oncology Nurse Navigator (ONN) Role Delineation Study that commenced in 2010 [34]. Findings of the ONN Role Delineation Study (RDS) were to provide a foundation for future ONS oncology nurse navigation-related programs and projects. RDS methods followed the process used by the Oncology Nursing Certification Corporation (ONCC) to develop eight nursing certification programs that currently certify nearly 38,000 nurses [35]. Three hundred thirty surveys completed by self-identified oncology nurse navigators (47 % of whom held one of ONCC's certifications) indicated tasks, knowledge areas, and skills viewed as essential to the oncology nurse navigation role, summarized in Fig. 2.1. This RDS failed to differentiate knowledge, tasks, and skills of oncology nurse navigators from those of other oncology certified nurses, an outcome

Tasks
• Provide emotional and educational support for patients • Practice according to professional and legal standards • Advocate on behalf of the patient • Demonstrate ethical principles in practice • Orient patients to the cancer care system • Receive and respond to new patient referrals • Pursue continuing education opportunities related to oncology and navigation • Collaborate with physicians and other healthcare providers • Empower patients to self-advocate • Assist patients to make informed decisions • Provide education or referrals for coping with the diagnosis • Identify patients with a new diagnosis of cancer

Knowledge areas	Skills
• Confidentiality and informed consent • Advocacy • Symptom management • Ethical principles • Quality of life • Goal of treatment • Therapeutic options • Evidence-based practice guidelines • Professional scope of practice • Legal and professional guidelines	• Communication • Problem solving • Critical thinking • Multitasking • Collaboration • Time management • Advocacy

Fig. 2.1 The top tasks, knowledge areas, and skills as rated by respondents to the ONS oncology nurse navigator role delineation survey

that was disappointing to nurses in navigation roles. Questions arising from the report of the RDS process and its findings relate to the definition of patient navigation as "individualized assistance," which could exclude knowledge and tasks relating to network-related tasks including community needs assessment, outreach, and other population-based tasks and activities described by Parker et al. [11] and Clark et al. [36].

Braun et al. [37] reported cancer patient navigator tasks across the cancer care continuum identified in five out of 25 NCI-supported Community Networks Programs serving underserved groups. The intent of their work was to clarify navigator tasks to "inform development of navigator programs, job descriptions, training, evaluation, certification standards, and reimbursement mechanisms" [37]. In this work, two frameworks, the continuum of cancer care and the five A's of quality care [38] (accessible, affordable, available, appropriate, and accountable), guided identification of key navigator tasks. The six phases of cancer care continuum identified by Braun and colleagues are as follows: (1) education and outreach, (2) cancer

Table 2.2 Navigator tasks across the cancer care continuum (Braun et al. [37])

Phase	Tasks
Phase 1: Education and outreach	Navigators use knowledge of the community to increase awareness of the value of early detection
Phase 2: Cancer screening	Navigators use different culturally appropriate approaches to increase screening among underserved individuals
Phase 3: Diagnosis and staging	Navigators help clients with suspicious screening results get cancers diagnosed and staged
Phase 4: Cancer treatment	Navigators perform tasks that reduce elapsed time between diagnosis and treatment and help individuals complete treatment and make the cancer care system accountable to the population
Phase 5: Survivorship	Navigators help individuals adjust to living with cancer and return to a regular cancer screening routine after treatment
Phase 6: End of life	Navigators can provide information to allow clients to make their own decisions, explore what they want of the future, and provide information about advance directives, palliative care, and hospice; link clients to other providers and spiritual and religious guidance as needed

screening, (3) diagnosis and staging, (4) cancer treatment, (5) survivorship, and (6) end of life [37]. Programmatic objectives in each phase of the cancer care continuum are described in Table 2.2.

The National Coalition of Oncology Nurse Navigators [20] and the Oncology Nursing Society [21] independently identified oncology nurse navigator core competencies. Similarities and differences between the two documents are apparent in Table 2.3.

2.6 Delivery System Structure and Support for Navigation Programs and Navigators

Throughout the first decade in which navigation programs were implemented, they grew in popularity, and observational studies offered encouraging outcomes. Early navigation programs offered services at no cost to patients, with no payment or reimbursement for those services. It was not unusual for a portion of navigation program funding to come from marketing and physician referral program budgets, designed to attract patients and retain them in delivery systems' networks. Navigation services at that time were supported largely by soft-funding sources – charitable donations, government, and industry grants – circumstances that create tenuous and unpredictable long-term sustainability. Many navigation services currently remain in this financial position.

Ongoing philanthropic and public funding is directed toward providing health-benefit, efficacy, and cost-effectiveness data to support patient navigation [39]. The National Cancer Institute's Center to Reduce Cancer Health Disparities and the American Cancer Society funded the Patient Navigation Research Program in 2005, with outcomes published in 2012 [40–42].

Table 2.3 Oncology nurse navigator core competencies

NCONN (2013)	ONS (2013)
1. Professional, legal, and ethical nursing practice The Oncology Nurse Navigator will integrate the philosophy of nursing care and evidence-based practice into care of the oncology patient	1. Professional role The ONN demonstrates professionalism within both the workplace and community through respectful interactions and effective teamwork. He or she works to promote and advance the role of the ONN and takes responsibility to pursue personal professional growth and development
2. Health promotion and health education The Oncology Nurse Navigator will perform an assessment of the patient's current health status to address health promotion need, functional status, developmental and lifestyle issues to maximize health outcomes. The ONN will implement specific therapeutic modalities to facilitate individualized care for the oncology patient in collaboration with the multidisciplinary team	2. Education The ONN provides appropriate and timely education to patients, families, and caregivers to facilitate understanding and support informed decision making
3. Management and leadership The Oncology Nurse Navigator will promote the role of patient navigation to the public market and health care industry to ensure preservation of the role and advancement of the profession	3. Coordination of care The ONN facilitates the appropriate and efficient delivery of healthcare services, both within and across systems, to promote optimal outcomes while delivering patient-centered care
4. Advocacy The Oncology Nurse Navigator will guide and direct the patient through a collaborative environment of health care disciplines to maintain dignity and autonomy of the individual patient	4. Communication The ONN demonstrates interpersonal communication skills that enable exchange of ideas and information effectively with patients, families, and colleagues at all levels. This includes writing, speaking, and listening skills
5. Personal effectiveness and professional development The Oncology Nurse Navigator will strive for optimal quality of nursing care through continued self-evaluation and program analysis that is adaptable to patient and community needs	

In a cooperative effort between Pfizer Oncology and the Healthcare Association of New York State (HANYS) and with consultation of Harold Freeman, the tool kit, *Patient Navigation in Cancer Care: Guiding Patients to Quality Outcomes*, was produced between 2006 and 2007 [44]. The kit contained four comprehensive manuals that offer guidance for establishing navigation programs using Freeman's

model: (1) *Establishing a Patient Navigation Program: An Implementation Guide for the Program Champion*, (2) *Navigation Pathways: The Patient Navigator Training Manual*, (3) *Colorectal Cancer Pathways: A Resource Guide for the Patient Navigator*, and (4) *Breast Cancer Pathways: A Resource Guide for the Patient Navigator.*

In 2009, the Association of Community Cancer Centers (ACCC) acknowledged acceptance of patient navigation services, asserting: "Patient navigation services can streamline patient access to care, enhance quality care, and increase both patient and provider satisfaction" [16]. In consideration of those potential outcomes, ACCC launched and made available to its members *Cancer Care Patient Navigation: A Call to Action* online resources [16]. This project was designed to help community-based cancer programs establish or expand navigation services. ACCC launched this project with stated intentions to:

1. Identify barriers to access to care that patient navigation can address
2. Increase successful implementation of patient navigation services
3. Refine staffing models
4. Establish effective metrics for measuring patient navigation services internally and for benchmarking patient navigation services against other community cancer centers.

Findings from small controlled trials of oncology patient navigation suggest improved time to diagnosis, downstaging at diagnosis, and reduced anxiety and greater levels of satisfaction among study populations. The effects of navigation on traditionally important cancer-related outcomes of survival, morbidity, and mortality are yet to be shown, but other metrics demonstrating cost-effectiveness are emerging. As these data are collected, analyzed, and demonstrate achievement of intended outcomes, patient navigation services increasingly become budgeted services in cancer care facilities.

2.7 Professionalization of Navigation

2.7.1 Social Workers as Navigators

In 1998, President and Mrs. George H. W. Bush invited more than 100 leaders from the collaborative public, private, and nonprofit sectors to participate in a "National Dialogue on Cancer," which evolved into the organization, C-Change, now with about 150 C-Change participants [45]. Its mission is "to eliminate cancer as a major public health problem at the earliest possible time by leveraging the expertise and resources of our unique multi-sector membership" [45]. C-Change supported the enactment of the Patient Navigator Outreach and Chronic Disease Prevention Act of 2005 [46] and provides ongoing support for patient navigation services. As a result of its active participation in C-Change, the National Association of Social Workers was an early professional association supporter of patient navigation.

The support provided by C-Change for the American Cancer Society (ACS) navigation model, in which "trained" lay navigators provide the service, was questioned by the National Association of Social Workers (NASW): language proposed by C-Change was (and still is) used in legislation, government and nongovernment grant programs, and other navigation-related initiatives. At issue was the absence of clear delineation of appropriate training, scope of duties, and the necessity of professional supervision (by social workers or registered nurses) of lay navigators. In 2007, the NASW concerns around lay navigator supervision had been resolved, and C-Change and NASW partnered to produce the *Cancer Patient Navigation Toolkit: A Guide to Community Navigation* to market the concept of patient navigation [47]. The NASW Foundation provided early research funding to analyze processes and outcomes of patient navigation. In an NASW Foundation-funded study reported in 2007, Ell and colleagues [48] devised and tested a structured clinical algorithm and demonstrated improved diagnostic resolution follow-up among low-income, ethnic minority women with abnormal mammograms as a result of applying the algorithm and patient navigation and counseling.

There is no evidence of strategic goals or initiatives on the part of NASW or AOSW after the joint position with the ONS was approved by all three professional organizations in 2010 [13].

2.7.2 Nurses as Navigators

Nurses in cancer patient navigation roles during the 1990s and the first decade of the twenty-first century had little to no support or guidance for their roles. There were, however, major questions and controversies: How is patient navigation defined? Should navigators be cancer survivors? Should navigators be nurses… or social workers… or physicians? How does someone become a navigator? What do navigators do? Who pays for navigation services? Does every person with cancer – or suspicion of cancer – need a navigator? Do navigators – or navigation processes – actually make a difference? The ONS would be a logical resource for oncology nurse navigators but did not take its first formal step in navigation issues until 2008 when a group of members in navigation roles formed a focus group – an informal prelude to an established ONS Special Interest Group (SIG).

In 2009, the ONS hosted a meeting of thought leaders affiliated with the ONS, NASW, and AOSW to develop a joint position statement to articulate a consensus opinion on the role of oncology nursing and oncology social workers in patient navigation. That joint position was approved by the three boards of directors in 2010 [13]. Key elements of the position include:

- Patient navigation processes are essential components of cancer care services.
- Patient outcomes are optimized with social worker, nurse, and lay navigator teams.
- Patient navigation programs must address underserved populations.
- Patient navigation programs must lay groundwork for sustainability.

- Nurse and social worker navigators function based on the scope and standards of practice for each discipline.
- Nurse and social worker navigators have education and knowledge in community assessment, cancer program assessment, resolution of system barriers, the cancer continuum, cancer health disparities, cultural competence, and individualized provision of assistance to patients with cancer, family, caregivers, and survivors at risk.
- Support must be provided for additional research to advance patient navigation processes and roles and to identify appropriate outcomes.
- Support is necessary for ongoing collaboration to identify metrics to clarify the role, function, and desired outcomes.
- Navigation services can be delegated to trained nonprofessionals and volunteers and should be supervised by nurses and social workers.

Two professional organizations, the National Coalition of Oncology Nurse Navigators (NCONN) and the Academy of Oncology Nurse Navigators (AONN), were established in 2008 and 2009, respectively, to address the educational, resource, and collegial networking needs of oncology nurse navigators. In 2010, NCONN had over 300 members. Member benefits included a very active Listserv and an annual conference with a navigation-specific focus. NCONN developed the first Oncology Nurse Navigator Core Competencies (Table 2.3) in 2009 and produced a revised version in 2013 [39].

AONN recently altered its original mission to include focus on lay navigators and the needs of cancer survivors:

> To advance the role of patient navigation in cancer care and survivorship planning by providing a network for collaboration and development of best practices for the improvement of patient access to care and quality of life [49].

Member benefits offered by AONN include discounted registration fees for regional and national conferences, access to online resources, and subscriptions to the AONN *Journal of Oncology Navigation & Survivorship*™ and other Green Hill Healthcare Communications publications [50]. Seven AONN chapters represent initial efforts to promote and facilitate networking and support at local and regional levels [51].

NCONN and AONN not only had similar missions and goals but also competed for the same membership cohort and corporate support and meeting sponsors. Both entities have histories of major support from for-profit marketing and educational groups. AONN+™ continues a long partnership with Green Hill Healthcare Communications, LLC [52]; NCONN's major sponsor for several years was Healthcare Professionals Network, a division of Intellisphere Oncology Specialty Group, a partnership that ended in 2012. In 2014, NCONN declared "mission accomplished" and disbanded, passed its core competency work on to ONS, and recommended its members support and participate in navigation initiatives directed by ONS [54].

2.8 Navigator Scope of Practice, Role Delineation, and Certification

According to the ONS/AOSW/NASW Joint Position, nurse and social worker navigators practice according to their respective scopes of practice [13]. The American Nurses Association describes professional nursing's scope of practice as the "'who', 'what', 'where', 'when', 'why' and 'how' of nursing practice" [54]. The discipline's foundational document, *Nursing: Scope and Standards of Practice*, explains that the profession has "one scope of practice that encompasses the full range of nursing practice, pertinent to general and specialty practice" [54] and assigns responsibility for developing scope and standards of professional practice to professional organizations. To that end, the ONS *Statement on the Scope and Standards of Oncology Nursing Practice: Generalist and Advanced Practice* [55] declares: "Oncology nursing practice encompasses the roles of direct care-giver, educator, consultant, leader, and researcher" [55] and extends to all care delivery settings. Principal goals of oncology nursing are to "promote cancer prevention and early detection and to facilitate optimal individual and family functioning throughout the disease continuum" [55]. Further, it is noted that oncology nursing practice, even at the generalist level, "requires a cancer-specific knowledge base and demonstrated expertise in cancer care" [55] beyond basic nursing education.

Similarly, NASW articulates social work scope of practice:

> Social work practice consists of the professional application of social work values, principles, and techniques to one or more of the following ends: helping people obtain tangible services; counseling and psychotherapy with individuals, families, and groups; helping communities or groups provide or improve social and health services; and participating in legislative processes. The practice of social work requires knowledge of human development and behavior; of social and economic, and cultural institutions; and of the interaction of all these factors [56].

The Association of Oncology Social Work identifies the scope of practice in oncology social work (2001):

> The scope of practice in oncology social work includes services to cancer survivors, families, and caregivers through clinical practice providing psychosocial services and programs through all phases of the cancer experience [57].

2.8.1 Navigator Certification

At the time of this writing, there is no recognized and accredited navigation credentialing process, although employers, organizations with navigator members, and individual navigators express interest in certification as verification of knowledge and skills necessary to successfully perform in navigator roles. However, certificate

programs, certificate of attendance or participation, certification processes, and the use of credentials and titles are often sources of confusion, misunderstanding, and misuse among employers, organizations, and individuals pursuing designation of specialized knowledge and expertise.

The Institute for Credentialing Excellence (ICE) defines "professional certification":

> The voluntary process by which a non-governmental entity grants a time-limited recognition and use of a credential to an individual after verifying that he or she has met predetermined and standardized criteria. It is the vehicle that a profession or occupation uses to differentiate among its members, using standards, sometimes developed through a consensus-driven process, based on existing legal and psychometric requirements [58].

Differentiation of professional certification, certificate program, certificate holder, and certificate of attendance is important. A *certificate program* is a "training program on a topic for which participants receive a certificate after attendance and/or completion of the coursework" [58]. Some certificate programs do require demonstration of attained course objectives. A person who completes a certificate program is acknowledged as a "certificate holder" but is usually not granted a credential [58].

Certificates of attendance, *participation*, or *completion* are "issued after an individual attends, participates in, and/or completes a particular meeting or course" [58]. Most often, no knowledge is assessed before such a certificate is issued, and such a certificate is not a credential since recipients need not demonstrate competence according to identified standards.

Several programmatic approaches claim to verify navigators' knowledge, skills, and competencies. The three programs mentioned here are exemplars of available programs and also provide a glimpse of the confusion generated by terminology employed.

2.8.2 Harold P. Freeman Patient Navigation Institute

The Harold P. Freeman Patient Navigation Institute (PNI) offers a patient navigation training program that awards participants certificates of completion [59]. Its curriculum includes five modules, case studies, and patient interaction practicum: topics include patient retention, diagnostic and treatment resolution rates, improved organizational efficiencies, and mechanisms to prevent lost revenue and contribute revenue to facilities [59].

2.8.3 The Breast Patient Navigator Certification Program

The National Consortium of Breast Centers (NCBC) is an interdisciplinary organization "committed to development, maintenance, advancement and improvement of quality patient-focused Breast Centers by supporting education,

certification and interdisciplinary communication among those served" [60]. The NCBC was the first organization to create a certification program to validate the skill sets of breast patient navigators and to thereby standardize the breast patient navigator's role. The first NCBC certification program was offered at its 21st Annual National Interdisciplinary Breast Center Conference in 2011 and currently offers six Breast Patient Navigator Certifications: The Certified Navigator – Breast in Imaging, Management, Advocate, Clinical, Provider, or Nurse [60].

Qualifications to sit for the NCBC exam include licensure as a medical professional – physician, registered or practical/vocational nurse, physician assistant, and social worker – and certification as a medical professional – radiologic technologist, radiology practitioner assistant, social worker, or advanced practice nurse [60]. Persons prepared at the master's degree level in a health-related field can apply to sit for this exam [60]. Applicants must have at least 2 years' experience navigating breast patients, must have navigated patients for at least 50 % of their job responsibilities, and must be NCBC members [60].

An initial step toward becoming a certified breast patient navigator (CBPN) through the NCBC program is the optional but encouraged attendance and participation in its day-and-a-half Breast Patient Navigator Certification Program, which provides information on the background of breast patient navigation, validity and importance of the role, and case study presentations and discussion [60]. The program also offers "certification examinations." Once attained, Breast Patient Navigator Certification is lifelong, although annual renewal ($50/year), submission of performance data, and eight CEUs with content on breast care and breast navigation and current NCBC membership are required to maintain active certification. NCBC claimed nearly 800 certificates among its six certification programs as of mid-2014 [60].

2.8.4 The Academy of Oncology Nurse & Patient Navigators (AONN+)

The AONN announced the development of a certification program and published a timeline to launch that extends to the first testing in 2016 with test results available in early 2017 [61]. The first certification examination targets general oncology nurse navigators – those who navigate oncology patients with any cancer diagnosis. According to details posted on the AONN website, the objectives of the certification program are twofold [61]:

1. To have oncology navigation recognized as a professional specialty by national, regulatory, and community organizations; nursing peers; physicians; institutional leadership; and patients and their families.
2. To establish baseline competencies for oncology navigators centered on their roles, responsibilities, educational level of knowledge, and evidence-based best practices that will help to ensure consistent delivery of optimized patient care across the care continuum.

Eligibility to sit for the AONN+ certification exam includes [61]:

- Current RN licensure
- Submitted job description and reference letter signed and dated by employer
- Curriculum vitae indicating a minimum 3 years of direct navigation experience
- Complete core curriculum course exam with a minimum passing score of 75 %
- Documentation of earned 15 CEUs in 2016

For various reasons, neither the NCBC's Breast Patient Navigator Certification Program nor the Academy of Oncology Nurse Navigators' Oncology Nurse Certification Program (as it is designed in 2015) meets nationally accepted accreditation requirements. "Core" features of certification programs accredited by the American Nurses Credentialing Center (ANCC) Magnet Recognition Program® [62], the National Commission for Certifying Agencies (NCCA) [58], and Accreditation Board for Specialty Nursing Certification (ABSNC) [63] are as follows:

- The certification addresses a professional body of knowledge, which typically has been defined in a scope and standards of practice.
- Development of the certification examination relies on:
  - A national job/task analysis (e.g., role delineation studies and content expert panels) that is periodically updated
  - Validation of generally accepted test development and psychometric principles
- A recertification interval is defined.
- The certification is available at a national level (i.e., it's not a state-based or system-based certification).
- The examination is not directly linked to a required course.

2.8.5 The Oncology Nursing Society and Oncology Nursing Certification Corporation (ONCC)

Encouraged by the ONS Nurse Navigator Special Interest Group, the ONS and ONCC undertook the Oncology Nurse Navigator Role Delineation Study (RDS) in 2011, with methods and findings published in 2012 [34]. The RDS, an initial procedure used to explore the feasibility of certification program development, is a formal process used to identify domains, tasks or competencies, knowledge, and skill needed to accomplish certain work. The ONS/ONCC Oncology Nurse Navigator RDS followed practices delineated and accepted by the Institute for Credentialing Excellence [34, 58]. As part of the RDS, an electronic survey was sent to the 280 members of the ONS Navigation SIG and members of AONN. The survey yielded 330 useable responses (50 %), a response rate considered highly acceptable for role delineation studies. The top tasks, knowledge areas, and skills associated with oncology nurse navigation, rated by survey respondents, are presented in Fig. 2.1. Based on these data, the RDS process failed to adequately differentiate tasks, knowledge, and skills

of oncology nurse navigators from other oncology nursing roles represented in the existing eight certification processes offered by the ONCC [34]. These findings do not lend support to investing significant resources for the development of a navigation certification program. One could argue that study design, methods, definition of terms, survey population, and instrumentation failed to depict the breadth and depth of the navigation role observed in earlier explorations of what navigators do [11, 36].

Since the publication of the navigation RDS, neither the ONS nor ONCC committed to substantial support for the evolving oncology nurse navigation role, until late 2015 when ONCC initiated a second role delineation effort. The ONS published the first book to focus on oncology nurse navigation – *Oncology Nurse Navigation: Delivering Patient-Centered Care Across the Continuum* in 2014 [64]. The Nurse Navigation Special Interest Group (SIG), now with over 2100 members, identified strategic goals for the years 2013–2016. Priority activities include [65]:

- Collaborate with ONS to define communication strategy for industry-wide promotion of ONN competencies as a standard of ONN practice.
- Advocate for formal recognition of Oncology Nurse Navigation as a subspecialty.
- Establish a joint ONS Corporate-Nurse Navigation SIG planning team to develop a training curriculum and certification/certificate.

2.9 Navigation Program Planning, Implementation, and Evaluation

2.9.1 Building the Evidence Base for Navigation Programs and Practice

When and where does a cancer patient navigation service make sense? There are no parameters to respond to this question. Health-care delivery system leaders could gather outcomes data associated with care and services currently available to people with cancer-related concerns throughout the continuum of cancer care and compare these data with norms and standards associated with quality cancer care. Findings serve as a gap analysis, revealing aspects of care and services that are lacking. For example, what is the follow-up from cancer screening programs? Do people with abnormal findings from screening return to the screening facility for additional diagnostic testing? At what stages of disease are patients diagnosed? Does diagnostic testing lead to treatment and follow-up in the same facility – or do patients go elsewhere for treatment? What is the time interval between suspicious screening findings to definitive diagnosis? And, what is the interval between definitive diagnosis and intiation of treatment? Can gaps in care and services be identified and can resources be made available to fill those gaps? What is the institutional impact of these gaps in care and services?

Desimini and her colleagues [66] in a Hospital Corporation of America (HCA) system compared reported benefits of patient navigation to gaps in care and services in their own facilities. Potential benefits included patients' needs for accurate information and

psychosocial guidance, increased patient satisfaction and decreased patient anxiety, decreased lengths of stay, reduced treatment delays, and financial return on investment [66]. They began by exploring why patients left the system after suspicious findings at breast imaging. Their analysis identified multiple factors associated with patients' decisions to go elsewhere for diagnostic procedures: lengthy lag time between screening and follow-up appointments, delays in receiving mailed reports, impersonal nature of receiving anxiety-producing news by mail, responsibility to make return appointments falling to patients, and the lack of protected diagnostic testing time slots for returning patients. As a result of these metrics, patient flow and process changes in these facilities were implemented, including systematic nurse navigator contact with patients within 24 hours of every screening mammogram, consistent provision of information to patients about additional views and other diagnostic procedures, and protected daily appointment slots for diagnostic testing to expedite scheduling of needed services [66].

The Catholic Health Initiatives Oncology Service Line *Navigation Program Resource* Guide [67] identifies four axioms to maximize the value of patient navigation, all important to navigation program planning, implementation, and evaluation:

1. Hire navigators and implement the program only when organizational needs are clearly identified, and the navigator role and desired outcomes are defined.
2. Navigators cannot "fix" all problems associated with strained cancer program operations: Program planners need to examine all processes and take steps to redress root causes of delays and gaps in care.
3. After process improvement, a needs assessment identifies patient and physician needs, gaps in care, operational bottlenecks, and market opportunities to inform navigation role development.
4. Implement quantitative measures to justify ongoing investment (i.e., tracking revenues from new and/or returned patients and navigator-specific patient satisfaction).

2.9.2 Navigation Program Champion

The "champion" role is essential to successful planning and program implementation [44, 68]. Navigation program development begins with the identification of a patient navigation champion – someone within the system who initiates and supports implementation of the program. The champion must be willing and able to commit time and energy to the tasks and challenges sure to be encountered. An effective champion is knowledgeable of health-care barriers, able to advocate for addressing gaps in care and services, and is a persuasive speaker and can articulate benefits of patient navigation to stakeholders and key decision-makers. The champion needs to provide compelling rationale based on demonstrated outcomes [44, 68].

2.9.3 Steering/Advisory Group

In a review of breast navigation program development at the Johns Hopkins Breast Center in Baltimore, Shockney et al. [69] describe stepwise program planning

processes that includes appointing a steering group in the initial planning stage, with representation of key stakeholder disciplines and a number of survivors serving as advisors. Through a consensus process, the steering group identifies needs to be addressed by the navigation program and desired outcomes to guide service planning and evaluation.

2.9.4 Community Needs Assessment

Cancer program planners and administrators need to assess the needs of the community to be served. From this assessment, program planners determine objectives and goals of navigation followed by considerations of the navigation model, navigator roles, and job descriptions most appropriate to meeting identified goals and objectives [69].

2.9.5 Navigation Model

Larger and more affluent systems may be able to accommodate a multidisciplinary navigation team composed of nurses, social workers, and lay navigators, in which navigators are assigned to a specific disease type that depends on the targeted population to be served – for example, breast cancer navigators, prostate cancer navigators, lung cancer navigators, GI cancer navigators, and/or hematology/oncology navigators. Smaller organizations often focus on a cancer type that is prevalent in the service area population. Many navigation programs initially focus on breast cancer among women and build on that programmatic experience. The actual needs identified determine the experience, skill set, and knowledge base required of the navigator(s): nurse, social worker, and/or lay community health worker or a team effort that combines the knowledge and skills each navigator brings to the program. According to Desimini and colleagues, a navigation model in which nurse navigator services are initiated at the earliest point in the cancer continuum "guarantees the patient the same healthcare contact in the event of a positive cancer diagnosis" [66]. This "entire continuum model" allows the nurse navigator to follow the patient from callback after suspicious screening findings to 12 months after diagnosis. Noted benefits of this model include:

- A consistent point of contact for the patient.
- It responds to patients' vulnerabilities and anxieties at the time of diagnosis and beyond.
- It provides patients with personalized coaching through testing, surgery, and additional treatment.
- It improves information sharing between patients and providers and among providers.
- It standardizes processes within and between care settings.
- Opportunities to retain diagnosed patients (or prevent outmigration) within the same health-care system [66].

After implementation of the entire continuum model of nurse navigators, Desimini et al conducted a four-year downstream analysis, noting an average $3000 greater contribution margin per patient due to procedures and services in the retained patient group [66]. Their analysis, demonstrated higher volumes of surgeries, infusions, radiation therapy, and imaging studies in the second two years of the navigation program. Instead of viewing navigation as an additional expense, this report attests to the importance of measuring and reporting the "return on investment" in navigator services by qualitative and quantitative methods over time [66].

2.9.6 Case Finding

The steering/advisory group establishes policy and procedures for case finding – identification of potential navigation patients, the point at which a patient enters the navigation program and the point when navigation services conclude [69]. For example, in a breast care program, a nurse navigator may be in constant communication with imaging services and is notified of scheduled screening mammograms and suspicious mammographic findings, at which point, the navigator contacts the patient to provide information about diagnostic testing, as well as facilitate and, in some cases, expedite next steps in diagnostic, work-up, and communication processes.

2.9.7 Scope of Practice and Job Description

The scope of practice among health-care professionals is defined by national professional organizations; state boards provide professional direction through practice acts; and specialty organizations establish standards relating to knowledge, skills, and competencies needed to perform within that specialty arena. Individual facilities and/or delivery systems devise job descriptions that meet organizational needs and are within the parameters of scope of practice. Typically, job descriptions identify titles, reporting structures, supervisory responsibilities, purpose of the job, and key responsibilities.

Despite nearly three decades of navigation experience reported in the literature, there has been minimal sharing of important foundational and consensus-driven documents such as role delineation, navigation program standards, best practices and associated outcome metrics, and navigator job descriptions. Job descriptions continue to be requested by nurses and social workers new to navigation roles, especially since so many arrive on the job with little to no structure or experience in the role, nor are there defined outcomes in place.

Newcomer [70] describes the process used by Catholic Health Initiatives' National Oncology Service Line (CHI NOSL), which supports some 40 cancer centers and employs more than 80 patient navigators, to create a national system approach to oncology patient population management and standardized navigation system-wide [67, 70]. The Newcomer paper includes the Job Description Template

and "addendum detailed responsibilities" devised by CHI NOSL that navigation programs are asked to adopt [70]. The CHI NOSL developed its comprehensive *Navigation Program Resource Guide* to "provide evidence-based recommendations for best navigation practices and to create a consistent approach to navigation across our CHI cancer programs" [67]. A revised and updated *guide* is expected to be made available. In the meantime, the initial CHI NOSL *Guide* is graciously made available on the ONS Nurse Navigator Special Interest Group website [67].

2.10 Navigation Program Evaluation and Outcome Measures

In 2010, few outcome metrics were available in published literature, yet policymakers and leaders in the navigation movement fully realized and embraced efforts to demonstrate value in navigation roles and navigation programs. In 2010, the American Cancer Society hosted the National Patient Navigation Leadership Summit, cosponsored by Pfizer Oncology, LIVESTRONG, Susan G. Komen for the Cure, the Oncology Nursing Society, the American College of Surgeons Commission on Cancer, the American Cancer Society, and AstraZeneca [71]. A collection of papers published as a supplement to the journal *Cancer* proposes common outcome metrics with which to measure the work of patient navigation [71, 72]. Ultimately, the intent of the Summit and subsequent Supplement was to help solidify the evidence needed to change policy and eliminate the "disconnection between discovery and delivery of services for all" [71], thereby securing the place of navigation in the US health system.

In a review of evaluation and outcome measures, Crane-Okada [73] identified 18 nursing research studies published between 2000 and 2010 and another 14 reports published in 2012. She differentiates evaluation and outcome measures: "evaluation" refers to assessments of whether patient navigation is implemented as planned; "outcome measures" consider the impact of navigation. Conclusions drawn from this review support the need for additional research to identify the range of oncology nurses' involvement in patient navigation, replication of findings of improved outcomes, and identification of the value added by oncology nurse navigators [73]. Surely, similar research questions could be posed for involvement of social workers in patient navigation, though such reports are not apparent in current published literature.

Swanson et al. [74] describe the National Cancer Institute Community Cancer Centers Program's (NCCCP) effort to develop *the Navigation Assessment Tool*. The Navigation Assessment Tool presents infrastructure and building blocks for starting a patient navigation program focused on creating high-quality, patient-focused processes that also offer a return on investment. A literature review and brainstorming sessions identified 16 essential core measures of navigation program development listed in Table 2.4.

Navigation program outcome metrics identified by CHI NOSL and published by Newcomer [70] include patient volumes, referral sources, timeliness to care (compared to national benchmarks), number of barriers to care or identified patient

Table 2.4 Essential core measures of navigation program development based on NCCCP multidisciplinary cancer program assessments

Core measure	Description
Key stakeholders	Buy-in from key stakeholders: • Navigators and cancer center staff • Cancer center administration • Physician involvement and support
Community partnerships	Entities inside and outside of the program that provide support for patients
Acuity system and risk-factor identification	Resources devoted to a patient depending on the individual's needs and risk factors – increase of risk from complications with the disease and cancer treatment
Quality improvement	Measures of sustainability: • Time to diagnosis • Time to treatment • Patient satisfaction • Cost-effectiveness
Marketing	Word of mouth, formal marketing with basic written materials, health fairs, and cancer screening events, targeted media sources to engage customers
% of patients offered navigation	Monitor progress to address barriers to care: determine appropriate denominator – i.e., all analytical cases, total number of abnormal screening
Continuum of care	Identification of contact points in patient navigation: • Abnormal finding to diagnosis • Diagnosis to surgeon visit • Transition from surgeon to medical or radiation oncology • Changes in treatment regimen or modality • Transition to survivorship
Support services	Identification of available support to be used by the navigation team in the system and/or through referrals
Reporting tools	Means of documenting navigation data
Financial assessment	Assessment to gauge patients' abilities to achieve best outcomes with least financial burden
Focus on disparate population(s)	Conduct cultural sensitivity assessment, creation of cultural objectives, on annual basis
Navigator responsibilities	Definition of navigator's level of responsibility and scope of accountability in an effort to focus efforts, resolve conflict, prevent burnout, and avoid unrealistic demands
Patient identification	Measures to identify patients: • Navigator reviews pathology reports • Navigator reviews procedure schedules • Navigator receives patient self-referrals • Navigator receives provider referrals
Navigator training	Ongoing training to excel in navigator core competencies: knowledge of patient experience and when and how to engage with patients
Engagement with clinical trials	In-depth education of benefits of clinical trials and participating in recruitment to trials
Multidisciplinary conference involvement	Navigators should attend and participate in tumor conferences to share information about patient care and support discussion of patient cases, assist in case finding presentation, and provide review with patients and families

Adapted from Swanson et al. [74]

needs, overall patient satisfaction, and provider satisfaction. Which metrics are important? Decisions around priority data collection and metrics will likely follow rationale used to justify implementation of a navigation program and navigation's purpose and roles.

Offered below is a limited overview of published papers that begins to fill the gaps in knowledge and evidence of outcomes linked to navigation. Reports included here are selected because they relate to the most common justifications for the implementation of navigation services.

2.10.1 Reduction in Health Disparities

Early patient navigation programs focused on eliminating barriers to ensure that all individuals with cancer received timely diagnosis and treatment [75]. In a 2011 overview of the potential of patient navigators in eliminating health disparities, Natale-Pereira et al. [76] contend:

> Patient navigators can not only facilitate improved healthcare access and quality for underserved populations through advocacy and care coordination, but they can also address deep-rooted issues related to distrust in providers and the health system that often lead to avoidance of health problems and non-compliance with treatment recommendations [76].

Outcome measures of navigation indicating effects on health disparities are offered in many published reports. However well-intentioned a navigation program may be, demonstration of economic and clinical value is crucial to decision-making about navigation program sustainability. Whitley et al. [77] propose five categories of care and cost measures useful to evaluate the economic value of patient navigation programs: program costs, human capital costs, direct medical costs, direct non-medical costs, and indirect costs.

Even as recently as 2012, few reports identify direct costs of implementing patient navigation programs. Jandorf and colleagues [78] carried out two randomized controlled trials to determine the effect of patient navigation on screening colonoscopy adherence and to assess economic impact of patient navigation from an institutional perspective. Average-risk minority patients referred to screening colonoscopy by primary care providers were recruited and randomized to one of four patient navigation groups. 395 patients completed colonoscopy, 53.4 % underwent colonoscopy alone, 30.1 % had colonoscopy with biopsy, and 16.5 % had snare polypectomy. The cost of patient navigation and net income to the institution throughout the duration of the study's data collection, were determined using routine cost analysis methods. Total revenue associated with these procedures was $95,266; total cost of patient navigation was $14,027, resulting in a net income exceeding $81,238. These authors concluded that patient navigation among minority patients generated additional income to the institution primarily because of increased colonoscopy completion rates [78].

The Cancer Disparities Research Partnership, an NCI-supported program designed to address inequities among American Indians (AI) in the Northern Plains region, assessed outcomes associated with two patient navigation strategies: navigators at a cancer center and navigators on reservations [79]. Throughout curative

radiation therapy regimens, the median number of AI-navigator interactions was 15; the median number of contacts between non-navigated AIs and provider contacts was four. Navigated patients averaged 3 fewer days of treatment interruptions compared to non-navigated patients. These researchers concluded that patient navigation is a component in addressing cancer disparities and supported the establishment of trust between AI patients and health-care providers, with tribal councils and the general population of three reservations [79].

Krebs, Burhansstipanov, Watanabe-Galloway et al. [80] describe an effort to decrease disparities exemplified by a patient navigation program for AI populations. Embedded Native Patient Navigators, in collaboration with local AI organizations, provided cancer education workshops designed to increase community knowledge and improve cancer screening behaviors. Outcomes of this community-based participatory study include increased community knowledge about cancer, increased cancer screening behaviors, increased visibility of navigators, and creation of an exemplar of successful collaborative efforts to eliminate barriers to care.

Gabram et al. [81] designed a cross-sectional study to assess outcomes associated with an outreach and internal navigation program on breast cancer diagnosis among urban African-American women. Their findings indicate an improved stage at diagnosis.

In a report from the Patient Navigation Research Program (PNRP), Freund et al. [82] reported combined analyses of nine of the ten PNRP centers. Analyses focused on the timeliness of diagnostic resolution in a meta-analysis comparing patient navigation (with lay navigators) with usual care among participants with breast, cervical, colorectal, or prostate screening abnormalities and/or cancers. Over 70 % of 10,521 study participants with abnormal screenings and 2105 with cancer or precancer diagnoses were from racial and/or ethnic minority groups, 40 % publically insured, and 31 % uninsured. Findings demonstrate no benefit from navigation during the initial 90 days of care but do note benefit for diagnostic resolution and treatment initiation between 91 and 365 days. From this study, its authors conclude that patient navigation is most beneficial in settings serving populations at risk of being lost to follow-up [82].

In another PNRP report, Bensink et al. [83] compare costs and outcomes of patient navigation (with trained lay navigators) versus usual care after abnormal screening. They found no differences in the average number of days to resolution or stage distribution among participants diagnosed with cancer. Navigated patients, however, were more likely to achieve diagnostic resolution. The added cost of navigation versus usual care was $275 per patient, leading to the conclusion that navigation is likely to be cost-effective when improved resolution translates to earlier cancer stage at diagnosis [83].

There is limited literature focusing on Latino populations. To address this gap, the federally funded Redes En Accion: The National Latino Cancer Research Network developed and tested a culturally tailored patient navigation model, the Six Cities Patient Navigation Study (San Francisco, San Diego, New York City, Miami, Houston, and San Antonio). Two studies, published in 2013 [84] and 2014 [85], analyzed time from breast screen abnormalities to diagnosis [84] and time to

initiation of treatment [85] among underserved Latinas. Using Freeman's navigation model, bilingual community health workers were trained to help Latinas in using cancer care services. According to findings in these studies, navigated women had shorter time to diagnosis [84] and reduced time to initiation of treatment [85].

2.10.2 Quality Improvement

As a quality improvement initiative, Basu and colleagues [86] analyzed timeliness of breast care consultation with and without nurse navigation in an academic comprehensive cancer center setting. Findings revealed no change in timeliness among nurse-navigated and non-navigated women 30–60 years of age, but timeliness was significantly shorter among nurse-navigated women older than 60 [86].

In a randomized controlled trial to determine outcomes of patient navigation on time to diagnosis, anxiety, and satisfaction among urban minority women with abnormal mammograms, Ferrante, Chen, and Kim [87] found patient navigation (by a navigator with a bachelor's degree in social relations and experience as a counselor, advocate, and breast support group volunteer) to be an effective strategy to shorten time to diagnostic resolution, lower anxiety scores, and increase patient satisfaction scores.

2.11 Improved Patient Experience, Distress Levels, Symptom Management, and Quality of Life

In a retrospective chart review of 55 inpatients with cancer diagnoses, Swanson and Koch compared distress scores of patients seen by nurse navigators with scores among patients not seen by nurse navigators [68]. Their findings of statistically and clinically significant lower distress scores among patients seen by oncology nurse navigators suggest patients benefit from oncology nurse navigator relationships and interventions.

Fillion and colleagues [88] report outcomes associated with professional navigator exposure among patients with head and neck cancers. They define *professional cancer navigator* as typically having a background in nursing or social work and possessing clinical expertise, communication and problem-solving skills, and broad knowledge of the health-care system [88]. According to these authors, the "professional navigation model is one in which the navigator goes beyond case management to a comprehensive medical or social model" that "values humanizing the care trajectory and empowering the patient and family" [88]. In this study, two demographically similar patient cohorts were compared according to exposure to the professional navigator or not. Patients in the navigator-exposed cohort had improved continuity of care, higher satisfaction and shorter hospital stays, fewer cancer-related problems, and better emotional quality of life [88].

2.12 Without Navigation?

Most available evidence seems to support the concept and operationalization of navigation, pointing to measureable outcomes of positive effects of these services. Harding and McCrone take a very different approach by exploring the experiences of non-navigated women undergoing breast diagnostic evaluation [89]. Using focus group structured interviews, their qualitative content analyses revealed three categories relating to supportive care: information, navigation, and communication. Participants described dissatisfaction with information received from providers and consequently, felt unprepared for diagnostic procedures, and lost trust in health-care teams. Difficulties accessing care and lack of guidance relating to where to go for treatment contributed to participants' anxiety and distress. Participants voiced dissatisfaction with the length of time between procedures; late, lost, and missing test results; and miscommunications among health-care teams. The lack of providers' acknowledgement of the stress experienced by participants, lack of compassion, false reassurances, and perceived dishonesty characterized patient-provider communication issues and contributed to participants' impressions of a dehumanizing experience [89].

2.13 Future

Despite global demands for *evidence-based practice*, demonstration of efficacy, and cost-effectiveness, patient navigation in cancer care emerged from the original Freeman model reports to present day, when patient navigation programs are increasingly an expected presence in cancer care settings. The American Cancer Society and the American College of Surgeons Commission on Cancer efforts are directed toward solidifying scientific evidence to change policy in favor of securing the place of patient navigation in the US health-care system. There is growing interest in oncology navigation in Canada and Europe [90, 91], Asia [92, 93], New Zealand, and Australia [93, 94]. Efforts are under way to apply navigation concepts and models to management strategies for other chronic diseases [95, 96].

As was acknowledged earlier, navigators cannot "fix" all problems associated with strained and dysfunctional delivery systems, and root causes of gaps and delays in care need to be addressed. Thorne and Truant suggest: "… navigation seems to have become the presenting symptom of a system with inherent ideological, cultural, and organizational problems" [8].

Communication is a core value among health-care professional education and delivery systems. Yet there is a long and disgraceful history of poor communication, collaboration, and cooperation among physicians and nurses [91]. More recently, reports emerge of adverse consequences of poor communications among and between health-care professionals, patients, family members, and informal caregivers. Poor communications are commonly root causes of fragmentation in care [97–99]. Patients still experience and suffer the effects of poor communications throughout the cancer trajectory [99, 100]. Notably, facilitating communication is consistently identified among tasks, behaviors, and competencies assigned to

navigators [20, 21]. Will introduction of navigators resolve and eliminate system-wide and/or interpersonal communication issues?

Thorne and Truant suggest the "enthusiasm for investment in navigation confirms the inherent value of the "invisible" work of nursing" and, further, that patients, planners, policy-makers, and administrators make the link between what is needed and what nurses are capable of delivering [8]. There is anecdotal information to suggest that the existing advanced practice clinical nurse specialist (CNS) role includes tasks, skills, and behaviors quite similar to those attributed to nurse navigators. Nurses with CNS experience prior to assuming navigator positions note similarities in the roles and expectations. Could this role be reconsidered and redesigned to perform as population-based specialists? It is likely too that social workers are equally underleveraged in issues around fragmentation of care and communications. Patient navigators will not repair dysfunction in health-care systems. Instead, strengthening and supporting the capacity of disciplines involved in cancer care, and leveraging knowledge and technology, could create health and cancer care systems so effective that designated navigators are not needed [8].

Navigation emerged as a relatively simple "fix" – simple, that is, compared to a complete overhaul of systems, infrastructures, processes, and personnel involved in cancer care delivery. Nearly three decades have passed since the concept of navigation was introduced. Governmental, nongovernmental organizations, policy-makers, industry, volunteer professional associations, advocacy groups, health-care leaders, individuals performing in navigation roles, and cancer patients and survivors are, by now, heavily invested in securing the place of navigation.

If it is truly the case that cancer care is so complex as to require this unique strategy and role, and that navigation is here to stay, a host of research questions must be explored for navigation to acquire a strong evidence base to support the role. Among them:

- What is the appropriate education, background, experience, and credential for lay and professional navigators?
- Is the navigator role analytically distinguishable from other cancer care providers?
- Is navigation a unique role within involved professional disciplines?
- Is navigation a subspecialty role of oncology nursing?
- Does (or how does) professional navigation differ from lay patient navigation?
- Is navigation effective in optimizing patient, provider, and system outcomes? Is navigation cost-effective? Can randomized trials provide rigorous evaluations of effectiveness?
- What variables predict timely outcomes in navigated patients?
- Is navigation an effective mechanism in the reduction of cancer health disparities?
- How does the scope of practice in defined navigator roles link to appropriate metrics to measure provided services?
- What definitions need to be drafted, accepted, and implemented to reflect local conditions and training, credentialing, and particular services provided by navigators?

Conclusion

Although many organizations and individuals enthusiastically support the concept of navigation, an underlying foundation has yet to be established. In summer 2015, the Oncology Nursing Society approved a new position statement outlining the role and qualifications of Oncology Nurse Navigators. According to this statement, nurses in "ONN roles should possess certification through one of the National Commission for Certifying Agencies–accredited certifications offered by the Oncology Nursing Certification Corporation—minimally, Oncology Certified Nurse (OCN®)" [101]. This, at least, opens a much needed and long overdue dialogue, and perhaps will pave the way for additional initiatives to identify the true nature and efficacy of this role and respond to existing and yet-to-emerge questions.

In the short history of patient navigation, there have been few signs of collaboration or evidence of an organized process to develop or provide consistency to the navigator role or navigation processes. Instead, the evolution of navigation is characterized by confusion and competition. The navigator role is informally and haphazardly created. Navigation has potential but, depending on how it is implemented, may or may not respond to the most important concern of patients and survivors throughout their cancer experiences: *Who will help me now?*

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Psychosocial Oncology

3

Karen Weihs

3.1 Introduction

Psycho-oncology is a specialized area of clinical practice and research that addresses the psychological and social well-being of cancer patients and their family members, as well as the integration of patient-centered care with the entire oncology treatment team. Psycho-oncology interventions contribute to cancer prevention, detection, treatment, and long-term survival. They optimize the ability of patients, their family members, and their healthcare team to understand their emotional responses, to think clearly about what they want for themselves, to align their behavior to reach these goals, to engage with others in the service of thriving to prevent cancer, and to adapt to cancer treatment and the survivorship experience.

Psycho-oncology is a young field. As treatment for cancer improved in the 1960s and 1970s, the first studies of psychological response to cancer were reported. Prior to these years, information about cancer was generally withheld from patients with the assumption that this was best for the patients' well-being, as cancer was still considered a terminal illness in most cases and a benevolent and paternalistic approach was considered best. The current context of patient and family engagement with the realities of diagnosis and treatment creates the need for psycho-oncology care focused on personal adaptation to cancer. More recently, the psychobiological aspects of interventions to optimize psychosocial wellness have

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begun to be investigated as possible adjuvant treatments to aid in curing cancer, making psychosocial oncology more relevant for the overall goal of cancer care to be curative and return patient and family to optimal functioning.

In this chapter, the following subjects will be addressed: (1) the nature of cancer-related stress, (2) adaptation to cancer-related stress and its complications, (3) psychosocial interventions to optimize adaptation to cancer and promote biopsychosocial health, and (4) integrated biobehavioral models of co-occurring changes in psychosocial adaptation and physiologic differences that may indicate synergistic mechanisms through which psychosocial well-being and disease outcomes are linked.

3.2 Stress in the Cancer Context

The diagnosis and treatment of cancer brings many stresses and burdens to the lives of patients, as well as to the lives of their family members and friends. It also brings opportunities for personal growth, for clarifying what matters in life, and for strengthening convictions about living with purpose. The resilience and resources available to people touched by cancer vary greatly, and provision of psychosocial care is best when it is tailored to the particular vulnerabilities and strengths of patients and their support systems. This is consistent with a growing approach to precision and personalized medicine.

Cancer does not occur in a vacuum, but within a life context that can be placid or fraught with non-cancer stressors. A married woman in her 40s with early-stage colon cancer whose adolescent children are well adjusted and whose spouse is employed in a high-paying and flexible job has a much different set of challenges than a woman of the same age with the same cancer who is a single mother working at a low-paying job and going to school at night. The availability of resources for coping with the demands of cancer, in the life context of the person and family compared to the demands on these resources, will shape the need for professional help during the cancer journey.

3.3 What Do We Mean by Stress?

Stress is a common and familiar part of life. Selye's definition remains useful to this day: "Stress is a process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological or biological change that may place the person at risk of disease" [1]. Cancer puts extensive demands on the lives of patients and family members. The severity of cancer and its associated stressors vary with the degree of *threat to the life course* of patients and their family members. The *life course of the patient and family* is manifest in its continuity over time [2]. It arises from their particular history and is guided toward the future by shared values and goals. Our concept of *threat* is informed by the work of Brown and Harris (1989) who designated the magnitude of threat based on the meaning of life events in the context of close relationships, personal history, and social

circumstances. They showed that the risk of depressive disorder was increased in proportion to the threat from stressful life events and difficulties defined in this way [3]. Measurement of the *threat to the life course*, therefore, is the best assessment of the stress in the cancer context because it is based on the effects of the specific experience of patients and their family members over time.

3.4 Psychosocial Adaptation to Stress in the Cancer Context: Vulnerability and Resilience

Emotional distress in response to disruptions of one's life course, such as receiving a cancer diagnosis, is normal. Resilient patients use this emotional reaction to focus their attention on the implications of this new situation for their life goals and to begin to adapt to them. Rather than avoid the initial emotional pain, they accept it as an important signal, providing information about a change to which they need to adapt. These resilient individuals call on their past experience of coping with life challenges, and they turn to trusted family and friends to help them process or "metabolize" the news, in preparation for adjusting their perspectives on their bodies, their sense of self, their roles in life, and their spiritual orientation. This is an active, effortful process and occurs over time, with the end result of a "new normal" being established for the patient and their close others. The new normal evolves over time as treatment unfolds and comes to an end or when the cancer progresses and the individual enters the chronic or palliative phase of cancer care.

Vulnerability to prolonged episodes of distress and less optimal adaptation occurs in individuals with preexisting patterns of emotional responding that either perpetuate the distress or bury it before it is processed. Rather than appraising the threat as circumscribed and specific, they generalize their sense of helplessness to all aspects of their new situation [4]. They are more likely to be younger and to have fewer close relationships that are secure and reliable [5]. Limited economic resources and less flexibility in their work and community environments increase the likelihood of non-metabolized emotional distress, which compromises their ability to think clearly and adapt their lives to the new demands of the stressful cancer context. When emotional and social resources are not available to mitigate the stressors of cancer patients, there is increased risk of adverse outcomes such as noncompliance with care, as well as the new onset of mental health problems.

Stress generation occurs when depression and anxiety resulting from overwhelming stress create the context for a cascade of new stressors. Maunsell et al. [6] found that women with stressful life events in addition to breast cancer have greater distress, depending on stressor magnitude. Burgess et al. [5] conducted a 5-year study of stressors in 170 breast cancer patients. Severely stressful difficulties predicted higher risk for major/minor depressive disorders or anxiety from 4 months to 2 years (RR: 1.36) and from 2 to 5 years (RR: 1.54), but not in the initial 4 months post-diagnosis. Low et al. [7] found that higher magnitude non-cancer-related events in the past year predicted more depressive symptoms concurrently and 6–12 months later.

The time course and style of adaptation to cancer vary with each patient's preexisting emotional, cognitive, and social resources. Oncology professionals and the patient's close others are well advised to accept differences in coping, such as a long initial phase of denial of distress and very limited disclosure of the cancer diagnosis to others in the patient's social network, in order to maintain empathy for the patient experience. Compassionate relationships provide the holding environment for patients to adjust their lives to the need for cancer treatment and offer an important opportunity for support and psychosocial interventions to be offered and accepted over time [8].

Post-traumatic growth occurs when patients and family members use adaptive coping strategies such as problem solving, positive reappraisal, active seeking of emotional support from others, and acceptance of aspects of the cancer situation over which they have limited control [9]. Resilient individuals pay attention to their emotions and share them with people they trust. Activation of attachment and caregiving drives within patients and their family members brings them together, promoting new awareness of their values and their ability to prioritize their efforts to maximize life satisfaction [2].

3.5 Developmental Differences in Adaptation

The developmental stage of patients and their families influences the nature and the extent to which cancer threatens their life goals [10]. For example, cancer in early childhood occurs in the context of acquiring skills of movement, cognition and communication, and learning to socialize with peers. Young families of children with cancer are establishing their identity, and the need to rely on grandparents interferes with the autonomous functioning and sense of control for the parents. Family disruption when a parent or sibling has cancer puts children at risk for regression from developmental milestones, increasing fears of being different from others and separation anxiety.

Rowland et al. outlined the developmental stages and their effects on adaptation to cancer, along with interventions to maximize childhood coping when a parent has cancer (Tables 10.4 and 10.7 from Holland in Blumenfield and Strain) [8]. Psychooncology interventions to preserve achievement of developmental milestones and to acknowledge their delay or loss when necessary can reduce the threat of overwhelming stress from cancer.

3.6 Clinically Significant Emotional Disorders Linked to Adverse Cancer Outcomes

Major depressive disorder is twice as prevalent in cancer patients attending outpatient oncology office visits as compared to the general population (6 % vs. 2 %), based on data from a recent screening study of over 20,000 oncology patients at all stages of cancer care [11]. Adjustment disorders, with persistent anxiety and

depressive symptoms that do not reach the threshold for major depression, nevertheless compromise functioning in up to 50 % of cancer patients. Fear of recurrence is reported by 70 % of cancer patients up to 5 years after diagnosis and probably longer [12]. Intrusive thoughts of cancer recurrence interfere with daily functioning in occupational, family, and community roles, although full-blown post-traumatic stress disorder is uncommon. Adjustment disorders with compromised emotional, cognitive, and social functioning are at least twice as prevalent in cancer patients as in people without a cancer diagnosis in the general population.

Depression heightens risk for morbidity and mortality in several chronic diseases, including AIDS and heart disease [13]. Although findings are not completely consistent, depression may confer risk for mortality in cancer [14], a relationship for which plausible biological mediators have been advanced [15]. Onitilo et al. [16] compared effects of depression on mortality in people with and without cancer in 10,025 participants in the National Health and Nutrition Examination Survey. After adjustment for confounders, people with both cancer and depression had a 19 % increased risk of death compared to people with cancer only. Mykletun [17] found a 33 % increased risk of death from cancer associated with disorder-level depressive symptoms in a prospective study of 61,349 adults in Norway followed for 4.4 years after depression assessment. Evidence that unremitting depressive symptoms are more pernicious for health outcomes than an acute depressive episode [18] underscores the importance of examining depression trajectories over time. A meta-analysis [19] revealed that depression, but not anxiety, triples the risk for nonadherence to a variety of medical regimens. Elevated depressive symptoms predict lower arm mobility [20] and lower satisfaction with medical care [21] over time in breast cancer patients. Medicare beneficiaries diagnosed with cancer are at least twice as likely to use emergency departments and medical inpatient services if they have significant depressive symptoms than if they do not [22]. In other chronic diseases, comorbid depression increases healthcare use, functional disability, and work absence [23].

3.7 Interventions to Facilitate Biopsychosocial Adaptation to Cancer

Many interventions to optimize psychosocial adaptation to cancer have been tested and found to be effective in high-quality randomized clinical trials over the past 40 years. A recent meta-analysis of interventions to reduce emotional distress and improve quality of life in cancer patients and survivors reported on 198 RCTs involving 22,238 patients [24]. This meta-analysis included only interventions delivered in person and included a range of psychological techniques, such as education, coping skills training, psychotherapy, and relaxation, alone and in combination, provided by professional therapists to patients with cancer. Significant small-to-medium effects were observed for individual and group psychotherapy and psychoeducation, and these effects were sustained for 6 months. Longer interventions were more likely to be sustained beyond 6 months.

Mindfulness-based therapy for symptoms of anxiety and depression has been studied over the past 10 years. A meta-analysis of 22 independent studies, including nine RCTs, found medium effect sizes (Hedges' g) of 0.60 and 0.42 in non-randomized pre-post design studies for anxiety and depression, respectively [25]. There was great heterogeneity of effect sizes between studies, likely due to differences in cancer type and severity, comorbid anxiety and/or depressive disorders, use of antidepressant medications, as well as level of motivation to practice between sessions, which is known to be associated with effects on symptom outcomes.

Most of these intervention studies targeted all patients with cancer, and because many cancer patients do not have high levels of distress, the pre-post changes across the interventions for the groups as a whole were modest. Larger reductions in distress were achieved when interventions targeted patients with elevated emotional distress or at significant risk for distress. Given the limited number of professionals trained to deliver psychosocial interventions to cancer patients, focusing resources on those with elevated psychosocial distress may need to be considered.

3.8 Identification of Emotional Distress in Cancer Patients and Family Members

Identification of clinically significant social and emotional disorders and their treatment by professionals with mental health training is crucial for restoring quality of life and facilitating full participation in lifesaving cancer treatments, yet professional oncology teams have commonly overlooked this area of patient care. Screening for psychosocial distress as a criterion for accreditation by the American College of Surgeons Commission on Cancer (COC) is required by the end of 2015. This requirement arose because the detection and treatment of emotional disorders is inadequate for cancer patients, resulting in suffering and worse outcomes [26, 27]. Only 27 % of those with documented major depression disorder (MDD) in a large screening study in outpatient oncology clinics in Scotland were receiving potentially effective treatment [11]. Pirl et al. [28] published recommendations for the implementation of distress screening, and the choice of which of several screening instruments to use is left to the judgment of the local cancer committee and the particular systems and personnel available to perform this task. These recommendations were developed by authors representing the American Psychosocial Oncology Society (APOS), the Association of Oncology Social Work (AOSW), and the Oncology Nursing Society (ONS) in which over 36,000 oncology social workers, psychologists, nurses, chaplains, psychiatrists, and other physicians who provide psychosocial care to patients with cancer in the United States are members. They emphasize that a plan for assessment and treatment of the detected distress must be in place prior to the initiation of screening. Oncology treatment providers who begin screening for distress must employ professionals who can intervene or who can effectively refer patients in need of mental health intervention to available providers of care.

Psychoeducation for patients with persistent anxiety or depression is crucial for overcoming stigma they may otherwise feel about being identified as needing

mental health intervention. The transition from identification to successful intervention for emotional disorders requires a coordinated professional team working in a patient-centered manner. Below we describe a collaborative professional model developed for use in the United Kingdom in which this transition has been successfully accomplished to the benefit of patients' mental health. In Chap. 4, *Management of Depression*, Fann describes collaborative care models that have been implemented in the United States.

3.9 Workforce Development to Address Psychosocial Needs of Cancer Patients and Families

Recent models of collaborative teams, including nurses, palliative care physicians, and oncologists, as well as more traditional mental health professionals, have begun to address the problem of undertreatment of psychopathology in cancer patients. The UK NICE Supportive and Palliative Care Improving Outcomes Guidelines [29] recommends a stepped care approach. Four levels of increasing specialization in psychological skills are described. At the first level, all healthcare professionals should have skills in effective information giving, compassionate communication, and general emotional support, as well as being able to recognize levels of psychological distress that are severe or persistent and require additional assessment and possible intervention. Training in these skills has been found to be most effective when offered in small groups focused on skill development [30]. At the next level, healthcare professionals are trained in simple psychological interventions such as problem solving to be used with distressed patients. Levels 3 and 4 require more formal training in psychosocial interventions, such as cognitive behavioral therapy (CBT). To address the limited number of oncology professionals with this formal training, Kath Mannix and Stirling Moorey created First Aid CBT training to increase the capacity of nurses and other palliative care providers to treat emotionally distressed cancer patients. Those treated by CBT-trained nurses had greater improvement in anxiety than patients whose nurse was not CBT trained. A dissemination project for training 120 palliative care nurses and physicians in First Aid CBT skills has been implemented across the United Kingdom (2009–2013) [31].

3.10 Ongoing Research: Studies of Biobehavioral Mediators of Psychosocial Intervention Effects of Host Physiology

A few studies have investigated the effects of psychosocial interventions on biobehavioral processes in cancer patients and then investigated the effects of these interventions on recurrence and mortality over the following 10 years [32–35]. For example, patients with malignant melanoma were randomized to 6 weeks of structured group-based psychosocial intervention vs. usual care [34]. Intervention participants revealed increased active coping and decreased negative mood at 6 weeks, increased interferon-stimulated natural killer cell cytotoxicity at 6 months and

decreased mortality and recurrence at 6 years [36], and 10-year follow-ups [35]. While the changes in biobehavioral processes at 6 months did not predict the 6-year clinical outcomes, intervention-associated increases in active coping did predict clinical outcomes. This suggested the possibility that other biobehavioral changes that may have occurred in tandem with increases in active coping (pro-angiogenic or pro-inflammatory processes) may have mediated the effects of this intervention on disease outcomes.

Andersen et al. [33] tested the effects of a group-based psychosocial intervention on survival and recurrence in 227 women with nonmetastatic breast cancer who received the intervention just after surgery. Women were randomized to standard care vs. 4 months of weekly group-based intervention and 8 months of monthly sessions. The intervention included relaxation and stress reduction exercises, coping skills training, and health behavior change strategies, related to diet and exercise. Intervention participants showed a significant reduction in overall and breast cancer-specific mortality rates as well as 45 % reduced risk of cancer recurrence at a median of 11 years follow-up. Those who did recur were cancer-free for an average of 6 months longer, after controlling for relevant cancer-related variables. Among those who died from breast cancer, the median survival time in the intervention group was 1.3 years longer ($M = 6.1$ year) than those assigned to standard care ($M = 4.8$ year). In addition to demonstrating effects of psychosocial intervention on clinical outcomes, Andersen et al.'s group has also provided some evidence for intervention effects on biobehavioral mechanisms that may explain these effects. Women whose cancer ultimately recurred revealed greater serum cortisol and greater levels of white blood cells and neutrophils 17 months prior to their recurrence, suggesting that these immunological changes may have been relevant in explaining differences in clinical outcomes between groups [37].

Andersen's team followed women after the point of disease recurrence and observed a reduced risk of death over an 80-month follow-up among those who had been assigned to the intervention arm [38]. During the 12 months following recurrence, the intervention group also showed improvements in psychological adaptation (decreased negative mood and increased social support) and greater lymphocyte proliferative responses to mitogens and greater natural killer cell counts. This trial provides the best evidence to date that a psychosocial intervention that improves psychological adaptation may increase cellular immune function early in treatment and decrease the odds of mortality and recurrence 7–11 years later.

Studies by Antoni et al. [39–41] have examined stress reduction techniques such as cognitive behavioral stress management (CBSM) and meditation-based stress reduction (MBSR) and have shown salutary effects on psychological adaptation, as well as neuroendocrine and immunologic indicators. In patients with cancer who received the interventions during their medical treatment, the effects of CBSM and MBSR have included decreases in late afternoon serum cortisol levels and increases in lymphocyte proliferative response and TH1 cytokine production as well as TH1/TH2 production ratio. Intervention effects on TH1 cytokine production may be important for supporting cellular immune processes that are involved in tumor eradication [42]. Recent publications by this group of investigators have demonstrated

differences in gene expression of circulating immune cells in breast cancer patients in a study of CBSM as compared to an educational control group. Pro-inflammatory cytokine genes were decreased, as were those involved in the metastasis-promoting epithelial-mesenchymal transition from normal cellular function to cancer. The link between psychological processes and cancer progression is suggested by these findings, as well as the capacity for psychosocial intervention to modify these mind-brain-body processes [43].

3.11 Future Directions

Recognition of the essential importance of biopsychosocial well-being to cancer outcomes, including prevention, treatment, and survivorship, is bringing attention to needed changes in the delivery of cancer care. Empowering patients and their family members with assessments of their stress-related risks and their personal resources for optimizing well-being can be integrated in healthcare delivery systems that emphasize patient education and close collaboration between patients and their providers. Patient navigators are likely to be helpful to patients for this purpose but will only be effective if they are fully integrated with social workers, nurses, psychologists, and physicians who can provide interventions for needs that are identified in the psychosocial domain.

Further investigation of stress-related physiologic changes in the cancer context, which can be identified early in the course of cancer detection and treatment, offers intriguing possibilities for a new domain of adjuvant cancer treatment. If neuroendocrine and immunologic processes supporting better outcomes are confirmed to be associated with regulation of social and emotional processes amenable to intervention, this will facilitate the closure of the current gap between psychosocial care and biomedical interventions. A future in which activated patients are supported by healthcare teams who function as truly patient-centered providers of care is likely to enhance the quality and, possibly, the quantity of life for patients and providers alike.

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Psychosocial Services/Management of Depression

4

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4.1 The Problem

Depression is one of the most common psychosocial problems encountered in the cancer setting. Within the context of newly mandated universal screening and provision of comprehensive psychosocial care that is integrated into the routine care of cancer patients, the American Society of Clinical Oncology (ASCO) has recently established clinical practice guidelines for the management of depression and anxiety [1]. The convergence of growing healthcare and health system complexity and clinical demands requires the development of integrated systems of psychosocial care that are cost effective and adaptable to diverse cancer care systems. While screening patients for depression has received primary focus, it is the subsequent steps, i.e., what to do with the information to best benefit the patient, that pose the most challenges. Research in oncology has confirmed findings in other medical settings that screening alone without an integrated system to ensure the appropriate

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triage, treatment, and follow-up of distressed individuals is not likely to be cost-effective in improving outcomes [2]. Toward the goal of patient-centered care and considering the often-daunting burden of multiple medications and medical appointments that cancer patients must face, healthcare providers must work with patients to negotiate a mutually agreeable treatment plan, taking into account patient preferences, and spend time to fully engage them in treatment. If adherence with treatment is poor, potential barriers to care or alternative treatment options should be thoroughly explored.

4.2 Evidence and Ongoing Research

4.2.1 Epidemiology of Depression in the Cancer Setting

Clinical depression is common in cancer patients and is frequently comorbid with other problems such as anxiety, pain, substance abuse, and suicidal ideation. Reported rates of depression vary widely in the literature, in part depending on whether the outcome is depression specifically or is evaluated along with other disruptions in mood such as distress, anxiety, or adjustment disorder. For example, in a recent meta-analysis, Mitchell et al. found that 30–40 % of oncology, hematology, and palliative care patients experienced some combination of mood disorder, including minor or major depression, anxiety, adjustment disorder, or dysthymic disorder. The authors found that results did not differ between palliative and non-palliative settings, and there were no consistent effects of age or gender [3].

Depression is associated with functional impairment, longer hospital lengths of stay, increased service use (e.g., emergency room visits) and costs, more physical complaints, lower quality of life, delayed return to work, desire for hastened death, increased mortality, [4, 5] and decreased acceptance/tolerance of and adherence to cancer therapy [6–8]. The role of depression on adherence is particularly salient in recently diagnosed younger patients for whom hormonal agents may be indicated, as these patients are less likely to desire hormone treatment [9].

When looking at clinical depression specifically in cancer patients, estimates of prevalence range widely between 5 and 50 % depending on the screening method, diagnostic criteria used, and timing of assessment. Most estimates fall between 5 and 25 % [10]. Unfortunately, few studies of prevalence of depression in cancer patients use a clinical diagnostic interview for depression. In a systematic review on this topic, Walker et al. found that of 66 relevant studies with an end point of depression in patients with cancer, only 15 met the authors' criteria for clinical definition of depression. In these studies, rates of clinical depression varied by setting, ranging from 5 to 16 % in outpatients, 4–14 % in inpatients, and 7–49 % in palliative care [11]. These wide ranges of reported prevalence underscore the need for further, high-quality studies of clinical depression in cancer settings and also the importance of vigilance for mood symptoms in patients at all stages of treatment. While some studies have suggested higher rates of depression in younger cancer patients, this

association has not been a consistent finding. However, gender-related differences in prevalence and severity have not been adequately evaluated in cancer patients [12].

Assessment of suicidal ideation in cancer patients is complicated by many factors, including an increase in reports of thinking about death and dying that might be normal in the context of a life-threatening illness. One study assessed responses to item nine of the Patient Health Questionnaire (PHQ-9) depression scale (thoughts of death or of hurting yourself in some way) and found that only 1/3 of 330 cancer patients who endorsed this item actually had thoughts of suicide, another 1/3 endorsed thoughts of death or dying but not suicide, and the final 1/3 denied any thoughts of death or self-harm on follow-up questioning [13]. Recent studies of risk of suicide in cancer patients reveal that the prevalence of suicidal ideation may be comparable to that of the general population, but prevalence of completed suicide is elevated in patients with cancer [14, 15]. A large retrospective analysis of Surveillance, Epidemiology, and End Results (SEER) data shows that the risk of suicide is highest in the first year, and particularly high in the first month, after cancer diagnosis [16]. Risk factors for suicide include those found in non-cancer populations, including clinical depression; sociodemographic factors such as male gender, older age, and lack of social support; and factors related to the patient's illness such as disease type and progression. Any patient with suicidal ideation should be promptly evaluated by a mental health specialist, and all clinicians should feel comfortable asking patients if they are having thoughts of death or self-harm.

Depression can be present at any point along the cancer continuum, from prediagnosis through treatment and into survivorship or end of life. Particularly vulnerable time points for depression in cancer patients include any change in disease or treatment status, including at diagnosis, when primary treatment has been completed (in survivorship), in the event of recurrence, or with disease progression [17–19].

The transition to end-of-life care may be a time of particularly high risk for depression [11, 20]. In one longitudinal study, depressive symptoms in patients with metastatic disease were three times more common in the final 3 months of life compared to a year or more before death. Risk factors for depressive symptoms in this group included younger age, antidepressant use at baseline, lower self-esteem, hopelessness, physical illness burden, and proximity to death [21]. A comprehensive, evidence-based guideline for preventing, identifying, and treating depression in European palliative cancer settings was published in 2011 and recommends early detection and diagnosis of depression, as well as regular reassessment [20].

Pathophysiology of depression in patients with cancer is likely multifactorial, with contributions from psychosocial and cognitive factors, pain, metabolic or endocrine abnormalities, medication side effects, and disease factors [22]. The field of psychoneuroimmunology may provide insight into high rates of depression and neurovegetative symptoms in cancer patients, and this has been a growing area of study in recent years. For example, a recent study of inflammation and behavioral symptoms in women who have had treatment for breast cancer supported a role for inflammatory processes (in particular, tumor necrosis factor-α signaling) in contributing to fatigue after treatment in these survivors [23]. Increased pro-inflammatory

cytokine levels resulting from tumor activity or treatment and acting on the central nervous system may partially explain the high rates of behavioral and affective symptoms such as depression, fatigue, anorexia, impaired concentration, sleep disturbance, increased pain sensitivity, and lethargy in patients with cancer. This syndrome has been called sickness behavior [23–26].

4.3 Solutions

4.3.1 Screening and Assessment of Depression in the Cancer Setting

A routine, systematic way of screening for depression is needed in the course of cancer treatment and should occur within the context of routine distress screening. If significant distress is detected on a global distress measure, further assessment should include an evaluation of possible depression, anxiety, insomnia, substance abuse, and other common comorbidities. Ideally, screening for depression should also occur intermittently throughout treatment, such as at designated intervals, during transitions in care, when a patient's condition worsens, or when psychosocial stress triggers increased need for support [27].

The Distress Thermometer (DT), which asks the patient to rate the severity of their distress on a 0–10 Likert scale, has been adopted by many oncology institutions as a global screen for distress. While a score of four or higher [28] has been suggested to signal a need for supportive care services, the DT has not been shown to have good specificity or positive predictive value for identifying depressed patients. Reports suggest that the DT is best used to identify those who are *not* depressed (i.e., scoring below four on the DT), with those scoring four or higher requiring further assessment with a validated depression screening instrument and/or a more thorough clinical assessment for depression [29].

Several depression screening instruments have been validated in the cancer setting [30]. An initial screen using one or two stem questions, i.e., for low mood and loss of interest, was found to have good evidence for case finding and screening, as well as high acceptability. The full PHQ-9 is a brief, self-report measure of depression symptoms that takes less than 5 min to complete. It includes the two stem questions for low mood and lack of interest, as well as other symptoms of depression [31], and is endorsed in the ASCO clinical practice guideline for depression. A recent analysis indicates that the PHQ-9, when scored as a continuous measure with a cutoff score of ≥ 8, has good sensitivity and specificity for identifying cases of major depression in cancer patients [32]. The PHQ-4, which assesses symptoms of depression and anxiety using the first two items of the PHQ-9 and the Generalized Anxiety Disorder-7 (GAD-7) questionnaires, can also be used as an initial ultra-brief screener. A positive screen on either the depression or anxiety section should result in the administration of the full PHQ-9 or GAD-7 [33]. The PHQ and GAD questionnaires are available in a variety of languages and have been widely studied cross-culturally.

Other somewhat longer measures of depression used in cancer settings are the 14-item Hospital Anxiety and Depression Scale (HADS) and the 21-item Beck Depression Inventory (BDI). The BDI is nearly as effective as a screening tool for depression in patients with cancer, as indicated by specificity and case finding, but has lower clinical acceptability than the one or two stem questions [30]. Similarly, the HADS has seven-item subscales for depression (HADS-D) and anxiety (HADS-A) and has been found to be a suitable screening instrument for depression and anxiety in patients with cancer, although with somewhat lower specificity and case finding than the BDI [30, 34].

It is important to note that the screening tools described above are not diagnostic of depression. Rather, they are intended to extrapolate pertinent clinical information which can identify patients in need of further clinical assessment. They have the added benefit of fostering dialogue with the patient related to current symptoms, concerns, and fears. Further, many of these instruments can be used as tools to monitor clinical course and treatment effectiveness. It is recommended that these screening tools be provided to patients to fill out electronically or in writing; if needed, they can also be administered verbally.

If depression is suspected, clinicians should complete a full assessment including diagnosis according to valid criteria (e.g., DSM-5 or ICD-10) and consideration of differential diagnoses including delirium, dementia, hypothyroidism, brain metastases, or adverse drug reactions. Psychological symptoms of depression including low mood, loss of interest in usual activities, feelings of hopelessness or guilt, or suicidal ideation are particularly important to attend to in cancer patients. Neurovegetative symptoms such as fatigue, appetite and weight loss, and sleep difficulty may be less reliable indicators of depressed mood in this population, as these symptoms may overlap significantly with disease or treatment effects. Depression should be carefully distinguished from sadness or grief about declining health; symptoms of depression are more constant, feel more permanent to the patient, and tend to impact the patient's enjoyment more pervasively [20]. Depression in the cancer setting should also be distinguished from demoralization, which is a sense of hopelessness or helplessness regarding purpose and meaning in life. Demoralization is present in 13–18 % of cancer patients at a clinically significant level and is associated with desire for hastened death, undertreated depression and anxiety, and reduced quality of life [35].

Identifying alcohol, sedative-hypnotic, corticosteroid, and opioid use is vital as these drugs may exacerbate depression, anxiety, and sleep issues in patients with cancer and can contribute to intended or unintended overdose. Validated screening tools for the most common substances of abuse include the ten-item Alcohol Use Disorders Identification Test (AUDIT or shorter three-item AUDIT-C) or five-item augmented CAGE questionnaire for alcohol use (focusing on cutting down, annoyance by criticism, guilty feeling, and "eye-openers") and the Drug Abuse Screening Test (DAST-10) for drug use. Similarly, patients may present with what appears to be diminished cognitive abilities, which may be secondary to depression, medications, chemotherapy, a primary neurocognitive disorder, or a combination of these. Cognitive challenges can complicate the clinical assessment process for depression.

Brief neurocognitive screening tools such as the Montreal Cognitive Assessment (MoCA) [36] may help the medical team determine if additional evaluation or neurocognitive testing is warranted.

4.3.2 Pharmacologic Interventions

Effectively treating behavioral and neuropsychiatric conditions can improve quality of life and possibly overall health and immune function in patients with cancer. Psychiatric problems in patients with adjustment disorders may respond rapidly to improvements of their pain, sleep, or medical situation. Demoralized patients may brighten and activate normally in response to visitors, family, and enjoyable activities.

Treatment of contributory medical conditions that can increase risk or worsen neuropsychiatric symptoms (e.g., insomnia, sleep apnea, pain, anemia, hypoxia, nicotine withdrawal) should be optimized. Due to the high rate of medical and psychiatric comorbidity, minimizing polypharmacy by using medications that address multiple conditions is recommended. For example, antidepressants may simultaneously benefit depression, anxiety, pain, and hot flashes; psychostimulants may benefit fatigue, depression, and cognition. Any medications with potential for worsening depressive symptoms (e.g., interferon alpha, interleukin-2, corticosteroids, anticholinergics, high-dose benzodiazepines or opioids) should be reduced or discontinued, if possible. Although epidemiological data are mixed, depression has been reported with use of certain chemotherapies (e.g., cytarabine, L-asparaginase, taxanes, vincristine) and adjuvant therapies (e.g., selective estrogen receptor modulators [SERMs]).

Although evidence suggests the efficacy of antidepressants in the cancer setting, data from randomized controlled studies in cancer settings is limited, particularly for treatment of major depression [5, 37]. Therefore, treatment choice should be guided primarily by pairing the patient's specific symptoms with a medication with the most appropriate pharmacologic properties. Medications that have been successful for treating any prior depressive episodes should also be given preference. Given their relative safety in combination with medical therapies and benign side-effect profile, the selective serotonin reuptake inhibitors (SSRIs) are usually considered first-line therapies for depression. Citalopram, escitalopram, and sertraline have the lowest potential for drug-drug interactions. Citalopram especially can cause a dose-dependent increase in the corrected cardiac QT interval (QTc). This has been associated in rare cases with the ventricular arrhythmia torsades de pointes. Risk is heightened with use with other medications with pro-arrhythmia risk, such as ondansetron, antifungals (posaconazole, itraconazole, voriconazole, fluconazole), tacrolimus, methadone, prochlorperazine, and promethazine. SSRIs have been found to decrease hot flashes which are common in chemotherapy-induced menopause, including in patients who are not depressed. However, in patients taking tamoxifen, medications such as fluoxetine and paroxetine that strongly inhibit the CYP450 2D6 isoenzyme should be avoided due to the potential for decreasing

the clinical efficacy of tamoxifen by lowering the concentration of endoxifen, the active metabolite of tamoxifen [38, 39].

"Dual-action" serotonin-norepinephrine reuptake inhibitors (SNRIs), venlafaxine and duloxetine, are also effective and may provide benefits for hot flashes, fatigue, and neuropathic pain related to cancer treatment [40]. Mirtazapine, another novel dual-action antidepressant, may be helpful for nausea and weight gain and is given at night due to its sedating effect. However, because some case reports have linked mirtazapine with rare cases of agranulocytosis, this agent should be used with caution in at-risk patients such as those undergoing cytotoxic chemotherapy. Bupropion, an activating and primarily dopaminergic agent, is often used to augment other antidepressants. Essentially devoid of sexual side effects, bupropion can help offset this common drawback of SSRIs and also has the added benefit of supporting smoking cessation. See Table 4.1 for suggested antidepressant dosage ranges and cautions.

Table 4.1 Antidepressants commonly used for depression in cancer settings

Antidepressant	Suggested target dosage range	Common side effects and cautions
Bupropion	200–400 mg divided (or bupropion extended release once daily)	Anxiety, agitation, headache, nausea, insomnia, seizures (rare)
Citalopram	20–40 mg daily	Nausea, headache, diarrhea, sedation, anxiety, sexual dysfunction. May cause decreased platelet aggregation, hyponatremia. Risk of QTc prolongation with dosages above 40 mg/day
Duloxetine	60–120 mg daily	Nausea or GI upset, headache, diarrhea, sedation, anxiety, sweating. May cause decreased platelet aggregation, hyponatremia
Escitalopram	10–20 mg daily	Similar to citalopram. Lower risk of QTc prolongation
Fluoxetine	20–80 mg daily	Similar to citalopram. Strong cytochrome P450 2D6 inhibition
Mirtazapine	15–45 mg daily	Sedation, orthostasis, dry mouth, weight gain, agranulocytosis/neutropenia (rare)
Paroxetine	20–40 mg daily	Similar to citalopram, sedation, weight gain. Strong cytochrome P450 2D6 inhibition
Psychostimulants, e.g., methylphenidate	5–30 mg divided	Insomnia, anxiety, agitation, tremor
Sertraline	50–200 mg daily	Similar to citalopram. Mild cytochrome P450 2D6 inhibition
Tricyclic antidepressants, e.g., nortriptyline	50–150 mg daily	Sedation, orthostatic hypotension, anticholinergic effects, arrhythmia, delirium
Venlafaxine extended release	150–300 mg daily	Similar to duloxetine, hypertension at higher dosages

Concomitant use of serotonergic agents with metoclopramide may increase risk for extrapyramidal reactions and neuroleptic malignant syndrome, and use with opioids such as fentanyl can increase risk of serotonin syndrome. Psychostimulants such as methylphenidate and dextroamphetamine can be an effective initial treatment when significant psychomotor retardation and fatigue are present, and more rapid activation, e.g., to promote treatment engagement, exercise, and nutrition, is needed while awaiting the benefits of antidepressants.

While antidepressants are generally well tolerated in patients with cancer, certain potential side effects warrant particular attention. Drug-induced neutropenia has been reported with some antidepressants, such as tricyclics, trazodone, and mirtazapine; it can be particularly problematic in patients undergoing chemotherapy and usually becomes apparent after 1 or 2 weeks of exposure. The severity of neutropenia that develops depends upon the dose and the duration of medication exposure. Antidepressants with highly potent serotonin reuptake inhibition (e.g., fluoxetine, paroxetine, and sertraline) have been associated with abnormal bleeding and altered platelet function. Interactions between antidepressants and antineoplastic agents that are mediated by CYP450 isoenzymes (particularly 3A4) can potentially compromise the effectiveness of cancer treatments or increase their toxicity [41]. Citalopram, escitalopram, venlafaxine, and mirtazapine are among the least likely to inhibit CYP450 metabolism.

4.3.3 Psychotherapeutic Interventions

Literature on the overall efficacy of psychological interventions in reducing clinical depression in patients with cancer is limited. There are few high-quality randomized controlled trials (RCTs) of interventions in patients with cancer with clinical depression specified as an outcome and measured using validated tools [5, 42]. Additionally, there is a lack of clarity in defining "psychological interventions" in the cancer literature [43]. In a systematic review of RCTs for depression in adult patients with cancer, Walker et al. found only eight published manuscripts (describing seven trials) that met inclusion criteria for the analysis. Only one was a trial of psychotherapy, which found that behavioral activation and problem solving were both effective in treating depression in patients with breast cancer [5].

While psychotherapeutic and pharmacologic interventions have been shown to be efficacious for depression in some studies, the effectiveness and potential harms of different treatment approaches for depression in cancer patients are largely unknown, underscoring the need for more comparative effectiveness studies [5, 37]. A common call is for improved quality of study design and reporting, clear definition of clinically defined and measured end points, and unbiased reporting of results.

Research supporting various psychotherapeutic interventions in specific groups of cancer patients has examined a variety of outcomes. In a systematic review of interventions for patients with gastrointestinal cancers, interventions including various types of psychotherapy as well as exercise and pharmacologic interventions

were generally found to be effective in reducing physical and psychosocial symptoms and improving quality of life [44]. In patients with colorectal cancers, various interventions were found to reduce length of hospital stay, days to stoma proficiency, symptoms of anxiety and depression, and quality of life [45]. In patients with prostate cancer, psychotherapeutic interventions have been found to improve the quality-of-life outcomes and increases in knowledge, but the clinical significance of these benefits is unclear [46].

The overall aim of psychotherapy in the oncology setting is to help patients improve coping strategies and promote adjustment to cancer diagnosis and treatment [37]. Other goals of therapy include reduction of distress, improvement of problem-solving skills, assistance in finding other sources of support, and reshaping negative or harmful thoughts. Additional benefits can be drawn from emotional support from the provider. Common therapies used with patients with cancer include supportive-expressive therapy, various types of cognitive behavioral therapy (CBT; including cognitive behavioral stress management and problem-solving therapy), and psychoeducational interventions.

Supportive, cognitive behavioral, and family or couples therapy are well supported by RCTs, reviews, and meta-analyses to be effective in reducing distress and improving quality of life in patients with cancer [4, 6]. In a meta-analysis of the efficacy of interventions for depressive symptoms in adults with cancer, Hart et al. evaluated ten RCTs with 1362 participants with mixed cancer types [4]. The authors found that five psychotherapeutic and four pharmacologic interventions were superior to control conditions for reducing depressive symptoms in adults with cancer (effect size $d = .42$). Interventions that were selected for elevated distress had larger effect sizes than those that did not select for elevated distress [4]. A meta-analysis of psychotherapeutic interventions targeting cognitive dysfunction in patients with various cancers showed no evidence of effect for reduced cognitive complaints but good support for improved quality of life [47]. Similarly, a systematic review of information provision and needs in patients with various cancers found that patients who were most satisfied had fulfilled information needs and experienced fewer information barriers, reported better health-related quality of life, and had less anxiety and depression; however, the authors found that reports of successful psychoeducational interventions aimed at improving information provision for patients are lacking [48].

One of the most effective behavioral interventions for patients with cancer may be promotion of physical activity. Exercise has been associated with improvements in physical and psychological function and has the added benefit of improving body image and health-related quality of life in patients with cancer [49, 50]. Across cancer types, exercise may have beneficial effects over time on fatigue and physical and social functioning. The authors found that positive effects of exercise interventions are more pronounced with moderate- or vigorous-intensity vs. mild-intensity exercise programs but concluded that further research is needed to determine how best to sustain positive effects of exercise over time and the essential attributes of exercise (mode, intensity, frequency, duration, timing) according to cancer type and treatment [51].

It may be particularly important to treat depression in the palliative care setting. There is little evidence supporting specific therapies in palliative care settings, but medications, CBT, problem-solving therapy, mindfulness techniques, and supportive therapies may all be helpful [20]. There is also growing evidence that quality palliative care itself may have significant psychosocial benefits. Early palliative care in patients with metastatic non-small cell lung cancer resulted in improved quality of life and less depression than in controls who received standard oncologic care alone. Patients in the early palliative care group had less aggressive end-of-life care but had longer survival [52].

4.3.4 Other Support Services

Patients and caregivers may experience a decline in emotional well-being, including an increase in depression, when barriers to treatment are not addressed and access to treatment or treatment engagement is impeded. Oncology social workers are often part of the multidisciplinary oncology team and can help manage the emotional, social, and concrete needs of patients, families, and caregivers. Social workers can provide navigational support and advocacy within complex medical systems, identify psychosocial or situational issues that may impair a patients' ability to engage in treatment, and help to coordinate referrals to other supportive services, such as psychiatry, psychology, chaplaincy, palliative care, and support groups. They may also provide direct counseling and emotional support to patients and family members on issues including grief and loss, communication with family/couples and medical providers, parenting and family concerns, substance use and co-occurring disorders, medical-legal documents, and practical issues such as transportation and financial assistance.

With social workers often being co-located within an oncology treatment setting, they can routinely connect with patients in person or by phone to provide information or support, such as following significant medical appointments where they may have learned of disease progression or a recurrence. In this capacity, they are in a good position to initially screen and identify patients who are in high distress and engage them in treatment [53].

4.3.5 Working with Families

There are 4.6 million Americans who care for someone with cancer at home [54]. A diagnosis of cancer can be overwhelming for both patients and family members, resulting in many lifestyle and role changes. While assessing the impact of cancer and treatment on the family, it is helpful to understand the patient's and family's baseline strengths and difficulties, as preexisting psychosocial and mental health issues may be exacerbated by a cancer diagnosis.

Psychosocial care that supports patients and family members in establishing routine pleasant activities and rituals, re-establishing roles, and creating family time for

communication and other activities can ease the burden of cancer and result in improved patient and family emotional and mental health [55]. Studies with non-cancer patients suggest that the presence of effective family caregivers can increase treatment adherence and improve overall care. For example, caregivers increase the probability of adherence to medication regimens, exercise protocols, and dietary recommendations, thus potentially diminishing the frequency and duration of hospitalizations. It is important to recognize, however, that a caregiver's negative emotional state, cognitive and physical impairments (including fatigue), and low literacy can impede their ability to accurately manage patients' medications [56].

A recent review of meta-analyses indicates that stress in caregivers can lead to psychological changes, sleep disturbances, and changes in physical health, immune function, and financial well-being. The authors note that when the patient and caregiver dyad is collectively treated, well-being of both parties is improved [57]. Research-tested interventions delivered to caregivers of patients with cancer have demonstrated reductions in many negative effects and improvements in caregivers' coping skills, knowledge, and quality of life. These interventions may also reduce patients' symptoms, lower mortality, and enhance patients' physical and mental health [57]. Most of the published studies on interventions for caregivers are psychoeducational in nature, providing information on helping to manage the patient's physical and emotional care. Other interventions focus on skills training (e.g., developing coping skills or training on couples' communication strategies) or therapeutic counseling. Although these studies tended to have small to moderate effect sizes, they consistently demonstrated improvements in both patient and caregiver physical and mental health outcomes [57]. Depressed mood in spouses of patients with breast cancer has been shown to have a negative impact on the patient's own functioning and well-being. Factors identified as risks for elevated depression in spouses of women with breast cancer include older age, less education, more recent marriage, elevated fears regarding their wife's well-being, worry about their job performance, uncertainty about the future, and poorer marital adjustment [58]. It is critical to attend to modifiable risk factors in spouses and caregivers of all cancer patients, as it is likely that earlier intervention and support will benefit the family member and the patient themselves.

4.3.6 Collaborative Care

4.3.6.1 Background

The Chronic Care Model, [59] which is an approach to integrated, patient-centered care of chronic illness, has been shown to improve clinical outcomes, processes of care, and quality of life in patients with chronic conditions such as asthma, congestive heart failure, diabetes, and depression. Key elements include the use of explicit plans and protocols; practice reorganization to meet the needs of patients who require more time, a broad array of resources, and closer follow-up; systematic attention to the information and behavioral needs of patients; ready access to necessary expertise; and supportive information systems.

A coherent system of supportive care is needed to efficiently target patient need as well as integrate with both oncology and primary care services. Use of navigators and care managers to coordinate care across services can eliminate fragmentation and increase efficiency. Recently, the Chronic Care Model has been specifically adapted as a model of quality cancer care. It emphasizes the need for an accountable practice team or care manager to ensure that the cancer care and psychosocial care are coordinated across the different phases of cancer and modalities of care [60].

The Chronic Care Model has been adapted to improve the management of depression and other mental disorders, leading to the development of collaborative care models. Collaborative care, which goes beyond merely "co-locating" psychosocial providers in cancer settings, is a practical way of delivering effective and integrated psychosocial oncology care. Core components of collaborative psychosocial oncology care include:

1. Delivery system redesign using integration of a centralized care manager to link patients; oncology, primary care, and psychosocial care providers; and other clinics or community resources. This often involves redefinition of work roles for clinical and support staff (Table 4.2).
2. Systematic, population-based approach to identifying needs and measuring outcomes using validated treatment response measures.
3. Electronic case registries to facilitate information flow and track critical clinical information for the caseload.
4. Strategies to engage, educate, and motivate the patient (and family) and monitor and enhance treatment adherence.
5. Brief, evidence-based, psychosocial treatments (e.g., problem solving, behavioral activation, cognitive behavioral therapy) provided by care managers.
6. Regular team caseload review and supervision of care managers by mental health specialists, including consultation for treatment nonresponders.
7. Stepped care management model providing intensified intervention to patients with inadequate clinical response.

Meta-analyses examining the effectiveness of collaborative care for depression in primary care have shown improved short- and long-term depression outcomes compared with standard care. Thota et al., in a meta-analysis of 69 trials, [61] showed robust evidence of effectiveness of collaborative care in improving depression symptoms, adherence and response to treatment, remission of symptoms, quality of life/functional status, and satisfaction with care. A systematic review of the economic efficiency of collaborative care for depression confirmed its cost-effectiveness and economic value [62]. Research has also shown that collaborative care programs that target both depression and pain can lead to greater improvements in both depression- and pain-related disability [63].

There is strong evidence that the collaborative care approach is adaptable across multiple mental health conditions, medical settings, and patient populations and provides a robust clinical and policy framework for care integration. A Cochrane review [64] of 79 RCTs of collaborative care for depression and anxiety,

Table 4.2 Members and roles of the collaborative psychosocial oncology care team in treating depression

Member	Roles
Care manager	Performs systematic follow-up clinical assessments to patients identified with depression. Links oncology team, consulting specialists, primary care provider, and support staff by enhancing communication. Motivates, activates, and engages the patient in depression treatment. Provides education to the patient and family around depression and other common comorbid conditions. Provides education to the oncology team regarding the nature and severity of depression and recommendations for management. Coordinates depression management plan with oncology team. Refers to community resources and follows up on referrals to increase rates of follow-through. Provides brief, evidence-based depression treatment (e.g., motivational interviewing for engagement, cognitive behavioral therapy, behavioral activation, problem solving, grief counseling)
Oncology team	Follows up on recommendations from the care manager and/or consulting psychiatrist/psychologist, including prescribing antidepressant medications under close guidance. Communicates any changes in patient depression levels to the care manager to facilitate the re-screening and follow-up process
Psychiatrist/psychologist	Provides supervision and weekly caseload review with care managers to recommend specific depression interventions. Identifies patients in need of more specialized consultation via the stepped care model and facilitates referral to the psychiatry/psychology service. Supports care managers and monitors for provider burnout. Provides regular training sessions to the care managers and oncology team to enhance provider education, particularly around medications and brief psychosocial treatments. Participates in institutional quality improvement initiatives and monitoring
Primary care provider	Communicates with the care manager and oncology team to provide patient history. Supports transition back into primary care after completion of active cancer treatment
Patient	Completes screeners and rating scales. Partners with treatment team in shared decision-making and implementing recommendations (including medications, counseling, behavioral strategies, and follow-up appointments) and tracking depression outcomes. Communicates any new concerns to the care manager and/or oncology team

representing a wide variety of settings, participants, medical comorbidities, and treatment modalities, found that collaborative care increases the delivery of guideline-concordant care and is effective in improving both short- and long-term outcomes across a broad range of healthcare settings, including underserved

minority populations. A meta-analysis of 57 trials [65] revealed significant effects of collaborative care across multiple disorders and care settings for clinical symptoms, mental and physical quality of life (QOL), and social role function, with no net increase in total healthcare costs.

4.3.6.2 Application of Collaborative Care in Oncology Settings

Because cancer centers are facing similar fiscal challenges as other healthcare systems, they must find ways to provide cost-efficient psychosocial care. While referral to community mental health providers for depression and other psychosocial problems remains an important option, many patient-, provider-, and system-level advantages exist for providing "in-house" psychosocial oncology services, when possible. For example, patients typically prefer to receive centralized healthcare, especially during intensive cancer treatment; providers benefit from comprehensive health records during complex treatment regimens; and care can be better coordinated within a single institution. These advantages, however, are counterbalanced against the costs of providing psychosocial care that is potentially resource intensive and often not revenue producing.

A viable solution to these challenges is the application of integrated collaborative care principles to the cancer setting, where collaborative care has several inherent advantages. First, oncology care in general embraces a culture of multidisciplinary collaboration. Second, collaborative care encompasses measurement-based care, the foundation of current oncology practice. Third, collaborative care has a history of working closely with primary care providers, which is a core component of cancer survivorship care. Fourth, collaborative care integrates well with the principles of many healthcare quality improvement programs. Finally, increased access to mental health facilitated by new legislation has created opportunities to provide mental healthcare to a larger number of patients.

At least six published randomized controlled trials have illustrated successful application of the collaborative care model, compared to usual care, among patients with cancer. The role of the care manager can be filled by nurses, clinical psychologists, or social workers. The unique patient populations and care settings in these studies highlight the flexibility and adaptability of the collaborative care model for use in diverse clinical oncology settings.

In the first three studies, stepped collaborative care for depression consisted of trained care managers who provided education, brief psychological treatment (problem-solving therapy), and coordination of care, including pharmacologic management, with medical/oncology providers. Caseload review and treatment supervision were provided by a team psychiatrist. The IMPACT study treated older adults with a cancer diagnosis and other medical comorbidities in 18 primary care clinics at eight diverse healthcare organizations across the US [66]. The Symptom Management Research Trial (SMaRT) Oncology-1 study treated cancer survivors in ambulatory cancer clinics in Scotland, UK, [67] and the ADAPt-C (Alleviating Depression among Patients with Cancer) used bilingual care managers and navigators to treat low-income, predominantly minority female patients in a public-sector oncology clinic [68]. All three studies showed both immediate and persistent

effectiveness of collaborative care, compared to enhanced usual care, for decreasing depression and improving quality of life beyond the intervention period.

As a follow-up to the SMaRT Oncology-1 study, multicenter studies in the UK, known as SMaRT Oncology-2 and SMaRT Oncology-3, were conducted in a large pragmatic cost-effectiveness trial [69] and in a trial of patients with lung cancer [70]. Both studies showed robust advantages of collaborative care over usual care for depression as well as an array of other important cancer-related outcomes, such as anxiety, pain, fatigue, functioning, and quality of life.

The INCPAD (Indiana Cancer Pain and Depression) trial utilized telehealth technologies to provide care management for depression and pain. Centralized nurses and depression and pain specialists provided collaborative care to 16 community-based oncology clinics throughout the state [71]. In addition to the scheduled telephone contacts, automated home-based symptom monitoring using interactive voice-recorded telephone calls or Web-based surveys were used to monitor outcomes and identify patients needing intensified treatment. Patients receiving the intervention had significantly greater improvement in pain and depression, demonstrating the viability of using telehealth and remote collaborative care teams to increase the reach of psychosocial oncology care for patients with multiple conditions.

4.4 Future Directions

Ultimately, innovation and flexibility will be required to develop effective adaptations and enhancements to the collaborative care approach to meet the needs of diverse oncology settings and ensure sustainability. For example, some centers may apply the ASCO clinical practice guidelines for depression by having care managers provide "first-line" management for mild to moderate depression, with clinic or community psychiatrists or clinical psychologists providing "stepped-up" care for severe or treatment-resistant cases. Technology can improve the provision of psychosocial care by addressing challenges such as the identification of patient needs as well as the provision of information, coordination of care, and psychosocial support while also potentially reducing cost.

One of the barriers to the implementation of the collaborative care approach in cancer settings, particularly in rural and remote areas, is the lack of availability of psychiatrists and other psychosocial specialists, particularly those experienced in treating cancer patients. Thus, the potential utility of telemedicine and video teleconferencing technology, coupled with task shifting and task sharing, in the context of the collaborative psychosocial oncology care model warrants further exploration. Having an option for community- or home-based treatment might also add efficiency, acceptability, and reach. Home-based collaborative care might be especially beneficial to patients with comorbidities or in end-of-life care that make clinic attendance difficult.

A framework for an integrated psychosocial model was presented in the 2008 Institute of Medicine report, "Cancer Care for the Whole Patient: Meeting

Psychosocial Health Needs." Despite the growth of evidence-based approaches for psychosocial care in the cancer setting, there remains a need for further implementation and dissemination research in diverse clinical settings that attends to "implementation outcomes" such as fidelity, penetration, sustainability, and uptake and costs as well as "service outcomes" such as efficiency, equity, patient-centeredness, and timeliness.

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Palliative Care

5

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5.1 Introduction

From the words "you have cancer," the life of an individual and their loved ones indisputably changes. Those few words have preconceived ideas of diagnosis, prognosis, treatment, and the "what now" questions moving forward. All of these concerns are legitimate and can be overwhelming. As much as healthcare providers may anticipate them, the discussions and symptom management are challenging for the providers, the patients, and their families. These challenging conversations continue to evolve along

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the cancer continuum. One such conversation may involve engaging the services of palliative care to better control symptoms, address concerns, and approach times of transition during the disease trajectory. It is not uncommon that the mere mention of palliative care evokes a sense of fear and hesitation in patients, families, and healthcare providers. Despite the growth of the field, the assumption remains that palliative care is synonymous with end-of-life care and that healthcare providers are giving up or abandoning all care, which is not the case. In the realm of oncology, palliative care is sometimes referred to as "supportive care." It encompasses symptom management in the broadest sense involving multidisciplinary teams and both palliative and disease-specific services as needed, initiated concurrently and provided in parallel from initial diagnosis and symptom management into transitions of care toward survivorship or end of life and bereavement. The term "supportive care" is speculated to be less distressing to patients, and oncologists are more comfortable with the word "supportive" as opposed to "palliative." Thus, "supportive care" resulted in earlier referrals to palliative care services and ultimately improved overall support and symptom management. When the palliative care program at the University of Texas MD Anderson Cancer Center was renamed supportive care, MD Anderson saw a significant rise in the number of referrals [1, 2]. Throughout this chapter, the terms palliative care and supportive care will be used interchangeably.

5.2 Definition of Palliative Care

Palliative care is both a philosophy and a system of care delivery of which hospice care is only one component. It was developed because hospice services were not sufficient as it was tailored specifically to the end of life. Palliative care, in turn, emphasizes providing support to the patient and family as a unit while offering symptom control and relief from suffering throughout the disease trajectory. This is a patient-centered approach compared to the customary disease-centered approach to care. Historically, palliative care has been defined in terms of four domains described by Cicely Saunders, the pioneer of the modern hospice and palliative care movement: the physical (symptoms such as pain, nausea, vomiting), the psychological (feelings of anxiety, stress, or worry), the social (family issues, economic constraints, and administrative planning), and the spiritual (ideas of transcendence and one's legacy) [3, 4]. Over time, these components have been formalized into a working definition of palliative medicine. The Clinical Practice Guidelines for Palliative Care in collaboration with the National Consensus Project provide the following definition:

> The goal of palliative care is to prevent and relieve suffering, and to support the best possible quality of life for patients and their families, regardless of the stage of disease or the need for other therapies. Palliative care is both a philosophy of care and an organized, highly structured system for delivering care. Palliative care expands traditional disease-model medical treatments to include the goals of enhancing quality of life for patient and family, optimizing function, helping with decision making, and providing opportunities for personal growth. As such, it can be delivered concurrently with life-prolonging care or as the main focus of care.

Palliative care is operationalized through effective management of pain and other distressing symptoms while incorporating psychosocial and spiritual care with consideration of patient and family needs, preferences, values, beliefs, and culture.

Evaluation and treatment should be comprehensive and patient centered with a focus on the central role of the family unit in decision making. Palliative care affirms life by supporting the patient and family goals for the future, including their hopes for cure or life prolongation as well as their hopes for peace and dignity including the dying process and death. Palliative care aims to guide and assist the patient and family in making decisions that enable them to work toward their goals during whatever time they have remaining. Comprehensive palliative care services often require the expertise of various providers to adequately assess and treat the complex needs of seriously ill patients and their families. Leadership, collaboration, coordination, and communication are crucial for effective integration of these disciplines and services.

5.3 Definition of Hospice

Hospice is an intensified form of palliative care during the last 6 months of life. It can be thought of as a subset of the palliative care delivery model utilized as a resource at the end of life. Hospice is described by the *National Hospice and Palliative Care Organization* as follows [5]:

> Hospice provides support and care for persons in the last phases of an incurable disease so that they may live as fully and as comfortably as possible. Hospice recognizes that the dying process is a part of the normal process of living and focuses on enhancing the quality of remaining life. Hospice affirms life and neither hastens nor postpones death. Hospice exists in the hope and belief that through appropriate care, and the promotion of a caring community sensitive to their needs that individuals and their families may be free to attain a degree of satisfaction in preparation for death. Hospice recognizes that human growth and development can be a lifelong process. Hospice seeks to preserve and promote the inherent potential for growth within individuals and families during the last phase of life. Hospice offers palliative care for all individuals and their families without regard to age, gender, nationality, race, creed, sexual orientation, disability, diagnosis, availability of a primary caregiver, or ability to pay.
>
> Hospice programs provide state-of-the-art palliative care and supportive services to individuals at the end of their lives, their family members and significant others, 24 hours a day, seven days a week, in both the home and facility-based care settings. Physical, social, spiritual, and emotional care is provided by a clinically-directed interdisciplinary team consisting of patients and their families, professionals, and volunteers during the last stages of an illness, the dying process, and the bereavement period.

5.4 Levels of Palliative Care: Primary, Secondary, and Tertiary Palliative Care

To some degree, palliative care is integrated into routine patient care by all clinicians. Specific scenarios and symptoms may require a more specialized approach to care. This can be likened to a primary care provider managing the majority of heart disease, while a subset of the population may need to see a cardiologist and a smaller subset may need to be treated by an interventional cardiologist. All levels support one another in the management of the patient's cardiovascular disease, but each provides a unique set of skills and expertise. In palliative care, primary palliative care is

provided by all healthcare practitioners. It is a set of basic skills and competencies routinely taught and practiced, allowing them to care for the day-to-day needs of the seriously ill. Primary care providers and oncologists are in key positions to provide primary palliative care given their established patient–physician relationship. Additionally, it is not sustainable for all palliative care needs to be referred for specialty care [6, 7]. Primary palliative care by primary care providers involves basic symptom relief, support and counseling, facilitation of advanced directives, and goals of care discussions [6]. The key tenants are to communicate honestly and effectively in a patient-centered fashion (establish the patient's understanding of their illness, prognosis, and treatment), evaluate the patient's goals of care, assess symptoms, strive to improve quality of life, discuss the overall needs of the patient and family including their spiritual needs, and formalize advanced directives [8]. In primary palliative care it is important to recognize and offer early referral to secondary palliative care and hospice services as a continuation of the care already being provided.

Secondary palliative care is provided by palliative care specialists, often in the form of consultation services. These are individuals with certifications and/or expertise in palliative care who can institute additional measures to improve quality of life and relieve suffering. This may occur in a variety of settings from an inpatient consult service, inpatient palliative care unit, outpatient palliative care clinic, to the home with home health services in conjunction with a community-based palliative care team. Likewise, hospice services may be provided in similar settings based on the patient's and family's wishes and needs [4].

Tertiary palliative care services often are in academic settings where specialized care is practiced, researched, and taught. There may be established training programs that also serve as examples to other healthcare institutions. Advanced expertise may include the use of implantable drug delivery systems, palliative sedation, controlling advanced delirium, and treatment of other severe or complicated symptomatologies [4, 6, 8].

5.5 Team Approach and Coordination of Services

The delivery of palliative care is a multidisciplinary team approach which utilizes individuals in a variety of realms both in and out of the traditional healthcare fields. This team approach emphasizes the importance of caring for the whole patient and their family as a unit. Members of the team include, but are not limited to, physicians, nurses, pharmacists, social workers, chaplains or spiritual counselors, physical and occupational therapists, and nutritionists [4] (Fig. 5.1).

With the many members of a palliative care team, there are a variety of different structures for the team. Bruera and Hui concisely outlined many of the common modes of palliative care delivery in their 2012 article [9]. For example, services can be delivered via a mobile consultation service in a hospital setting. The team in this setting often involves a physician, an advance practice provider, and physicians in training (medical students, residents, and fellows). Another mode is the acute palliative care unit where an interdisciplinary team cares for the acutely ill and actively dying and those whose family members need respite. Outpatient palliative care services for ongoing symptom management and goals of care discussions are

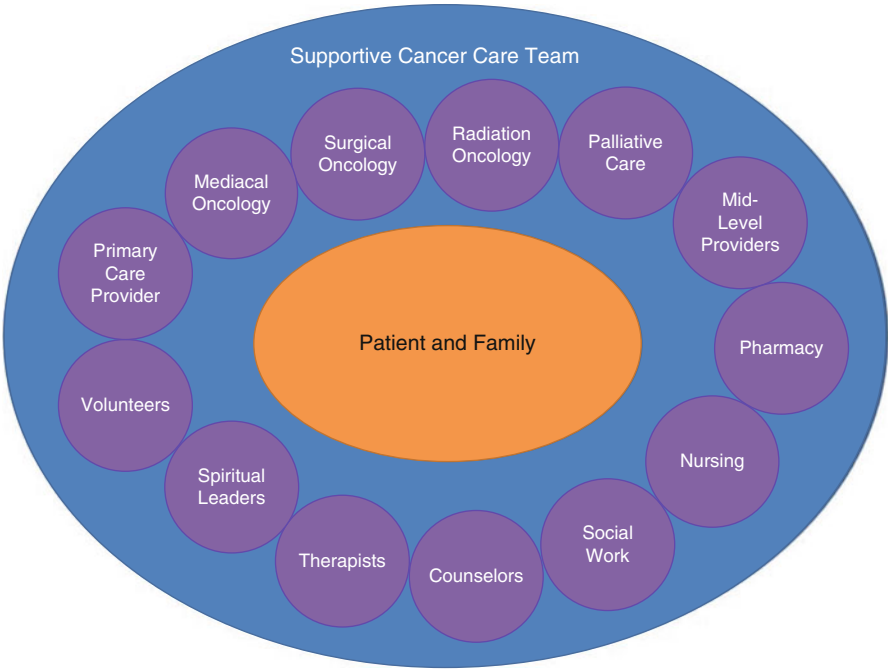

Fig. 5.1 The multidisciplinary team to provide support to the patient and family (Created by Briana Ketterer, MD)

becoming utilized more frequently. In this arena there are various different models of care delivery utilized. Most specifically we will address how supportive care and palliative care can be integrated into a comprehensive cancer care model.

Bruera and Hui described three practice models: the Solo Practice Model, the Congress Practice Model, and the Integrated Care Model [9]. In the Solo Practice Model, the oncologist provides both cancer care and supportive care. Time constraints of a busy practice, complex patients, and lack of formal training in palliative care often mean that not all components are adequately addressed, rendering this model less than ideal. In the Congress Practice Model, the oncologist refers to various services with special expertise. This can result in disjointed care at a great cost in time and money as well as patient access problems. Again, this model is less than ideal. The Integrated Care Model approaches an ideal system. The oncology team works frequently with the palliative care team for symptom management and develops a more coordinated approach to patient-centered care [9].

5.6 Referral to Specialty Palliative Care

Palliative care should be viewed as an adjunct to, not an alternative to, the management of life-threatening illness. By working together as an integrated unit throughout the disease trajectory, this could minimize patients' feelings of abandonment later in the disease course [10]. Early palliative care involvement in cancer-related care is

advocated by the National Comprehensive Cancer Network (NCCN) and reflected in national guidelines. Palliative assessment at the time of the life-altering diagnosis and utilization of palliative care services early in the disease course have been shown to improve quality of life measures, patient and family satisfaction, symptom management, and psychosocial support and ease the transition to end-of-life care [1]. Early palliative care, in addition to oncologic standard of care, improved quality of life measures and mood and prolonged survival in patients with non-small cell lung cancer despite less aggressive end-of-life care [11]. At a time when healthcare cost discussions abound, palliative care services lessen costs on the healthcare system especially during the last months of life without compromising quality of care and mortality [12].

According to the Institute of Medicine, regular screening by oncologists and other providers for the following should prompt palliative consultation: uncontrolled symptoms, moderate to severe distress regarding diagnosis or cancer-related treatment, comorbid conditions, life expectancy of less than 6 months, metastatic solid cancer, concerns about disease and/or decision-making process, assessment of caregiver burden, or requests for palliative involvement [13].

The NCCN outlines the following criteria for consultation in the NCCN Clinical Practice Guidelines in Oncology: Palliative Care [14].

Adapted from NCCN:

Palliative care 2013 criteria for consultation with palliative care specialist:

1. Patient characteristics:
   (a) Limited treatment options
   (b) High risk of poor pain control that remains resistant to conventional interventions
      (i) Neuropathic pain
      (ii) Incident of breakthrough pain
      (iii) Associated psychosocial and family distress
      (iv) Rapid escalation of opioid dose
      (v) History of drug or alcohol abuse
      (vi) Impaired cognitive function
   (c) Non-pain symptoms that are suboptimally controlled by conventional management, high symptom burden
   (d) Frequent ED visits or hospital readmissions
   (e) Complication ICU admissions (esp. lengthy ventilator support)
   (f) Multiple “allergies” or history of multiple adverse reactions to pain and symptom management interventions
   (g) High distress core (>4)
   (h) Cognitive impairment
   (i) Severe comorbid conditions
   (j) Communication barriers
   (k) Request for hastened death
   (l) Inability to engage in advance care planning and care plan
2. Social circumstances or anticipatory bereavement issues:
   (a) Family/caregiver limitations
   (b) Inadequate social support
   (c) Intensely dependent relationship(s)

(d) Financial limitations
(e) Limited access to care
(f) Family discord
(g) Patient's concerns regarding care of dependents
(h) Spiritual or existential crisis
(i) Unresolved or multiple prior losses

3. Staff:
   (a) Compassion fatigue
   (b) Moral distress

Another approach for healthcare providers to aid decision making regarding palliative care consultation is to consider the "surprise" question: Would I be surprised if this patient died in the next year? [15] Asking the "surprise" question does not require that we set an exact time frame, but instead draws attention to the fact that there are additional resources including palliative care services that may benefit the patient and family if we would not be surprised if the patient died in the next year. Similarly, if the provider would not be surprised if the patient died in the next 6 months, hospice services may be an option. Palliative care services should be considered early and often. Primary care providers, oncologists, and other frontline providers should have adequate training to provide primary palliative care and be able to recognize when specialized services are necessary. In addition, healthcare providers should advocate for expansion of palliative care services if such resources are absent or inadequate at their facility.

5.7 Standard of Care

Our current healthcare structure is often inadequate in meeting the needs of seriously ill patients. As discussed in the previous section, emerging evidence has shown that the introduction of palliative care improves quality of life, decreases symptom burden, improves mood, and decreases use of healthcare services [16]. As a result, the Institute of Medicine's 2013 report cites the lack of palliative care as a major problem in delivery of oncologic healthcare. An expert panel of the American Society of Clinical Oncology (ASCO) [17] and the NCCN guidelines state that institutions should develop processes for integrating palliative care into cancer care, both as part of usual oncology care and for patients with specialty palliative care throughout the different phases of care including diagnosis, treatment, survivorship, end-of-life care, and bereavement [18]. At least 85 % of hospitals with more than 300 beds and 98 % of cancer institutes have implemented palliative care programs according to the Center to Advance Palliative Care.

5.8 Quality of Life

Quality of life is influenced by physical, social, psychological, and spiritual dimensions [19, 20]. The concept of total pain described by Ferris and colleagues expanded to include eight domains of suffering in patients and family (Fig. 5.2) [21]. These eight domains included disease management, physical, psychological, social,

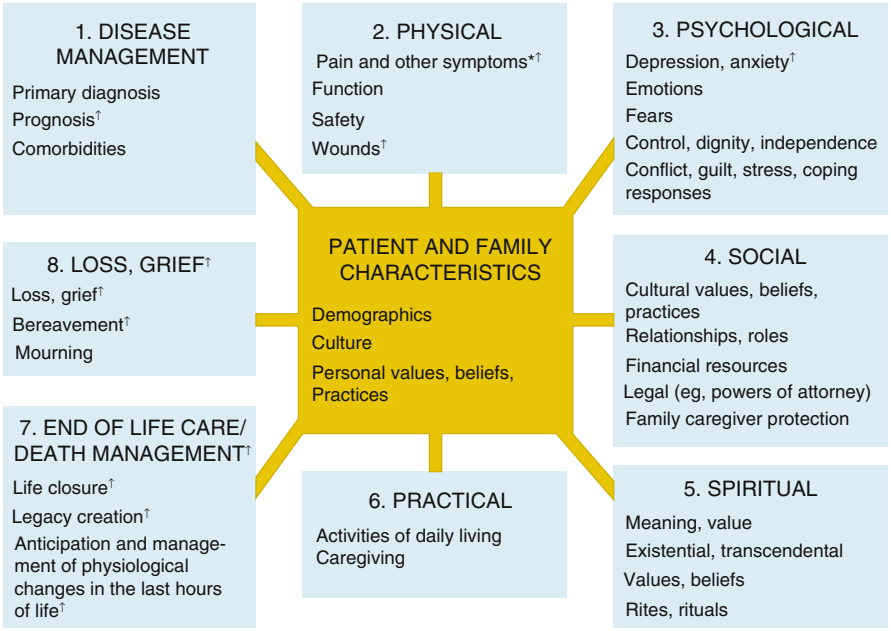

Fig. 5.2 Multiple issues that cause suffering (Reproduced with permission from Ferris et al. [17])

spiritual, practical, end of life, and grief [21]. All eight of these domains should be addressed to manage suffering and improve quality of life [21].

Quality of life is subjective, unique, and multidimensional. It can be difficult to measure, yet attention to quality of life is extremely important. Quality of life assessment can be helpful in weighing the risks and benefits of treatment options, particularly when differences in survival among the options are potentially small or unknown [22]. There have been many measures created to help quantify quality of life including the Missoula–VITAS Quality of Life Index (MVQOLI), the Palliative Care Quality of Life Instrument (PQLI), Life Evaluation Questionnaire (LEQ), the Brief Hospice Inventory, and the quality of life at the end of life (QUAL-E) [23].

In healthcare, the focus is on health-related quality of life (HRQOL) which is based on symptom burden and functioning and to a lesser extent on meaning and fulfillment. Patients with advanced cancer do frequently experience pain, fatigue, weight loss, anorexia, nausea, anxiety, shortness of breath, and confusion [24]. Yet as one approaches end of life, spirituality issues become more prominent, as well as family members' perception of quality of care. Thus it is very important to manage the family as the unit of care.

There is a rapidly expanding body of evidence that palliative and supportive care improves symptoms and quality of life for patients with cancer. Temel et al. reported that patients receiving palliative care had better quality of life and less depressive symptoms (16 % vs. 38 %, $P=0.01$) [11]. An advanced practice nursing palliative effort concurrent with usual care was successful at improving quality of life and

mood, though not symptom intensity or use of acute care [25]. Through an outpatient supportive care clinic for patients with advanced cancer, pain was decreased by 52 % and fatigue by 44 % [26]. An inpatient trial in Italy studying specialty palliative care teams found that risk of suffering from severe pain was reduced to 31 % by the use of palliative specialists [27]. A cluster randomized trial of Canadian cancer patients receiving early specialized palliative care in an outpatient clinic setting demonstrated non-significant improvements in quality of life at the primary end point and significant improvements at later end points [28].

5.9 Patient and Family Satisfaction

The SUPPORT trial was one of the first trials to demonstrate the lack of patient and family satisfaction in end-of-life care. Patient–physician communication was lacking and 50 % of patients suffered from moderate to severe pain which was not well controlled [29]. Patients with serious illness often develop depression, anxiety, and other mental health problems, but this is not limited to just the patient [30]. Caring for a loved one with a serious illness is stressful and is often also associated with depression, anxiety, and other health problems with their family caregivers [31]. This can have an impact to their perception of good quality of care and can lead to mistrust of their physician if these symptoms are not well managed [30, 32]. Steinhauser et al. surveyed terminally ill patients, recently bereaved family members, physicians, and other care providers to determine those factors deemed most important at the end of life. This highlights the deficits of the traditional medical approach to patient and family, which can leave out important considerations of care affecting patient and family satisfaction.

Palliative care focuses on enhancing communication and discussing goals of care early in the disease trajectory and thus elicits treatment plans that are in accordance with patient's goals early in the disease course. This intensive communication results in a higher level of patient and family satisfaction and smooth coordination of care between settings. Among family members of patients who died at one tertiary care hospital (which included 21 % [32/149] of patients with malignancy), Gelfman and his colleagues showed 65 % of palliative care patients' family members reported that their emotional or spiritual needs were met, as compared to 35 % of usual care patients' family members ($P = 0.004$) [33].

5.10 Cost Savings

Cost savings from palliative and supportive care comes largely from better matching goals of care and prognosis with desired intensity of care. Twenty percent of cancer patients receive chemotherapy within the last 2 weeks of life [34]. In the SUPPORT trial, end-of-life care caused bankruptcy in one-third of families, and the financial burden of that care did not equate to better quality of care nor better patient or family satisfaction [29]. According to a study in Critical Care Medicine, adding

palliative care shortened ICU length of stay. ICU length of stay was 5.72 days for group receiving palliative care vs. 14.12 days in the usual care group, a statistically significant difference of 8.40 days ($P = 0.004$) in this study of high-risk critical care patients which included 33 patients with stage IV malignancy [35]. Among women with platinum-resistant ovarian cancer, a palliative care intervention resulted in cost savings of $1285 per patient [36]. Less intensive or lengthy hospital stays result in cost savings overall.

5.10.1 Quality of Care

In response to the Institute of Medicine report, "Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis," the American Society of Clinical Oncology (ASCO) Quality Oncology Practice Initiative (QOPI) selected several key metrics for determining high-quality end-of-life care. These included: no chemotherapy in the last 14 days of life, enrollment in hospice services, and hospice length of stay of greater than 7 days [16, 34, 37]. These metrics track appropriate transition to hospice services which provide superior patient and family satisfaction, control of physical symptoms and mental health concerns, and less complicated bereavement [38]. The spring 2014 QOPI measures included (among others) metrics for:

- Location of death
- Whether death occurred with or without a hospice or palliative intervention
- Discussion of hospice or palliative care in the last 2 months of life
- Assessment and treatment of pain and/or dyspnea documented
- Antiemetic therapy prescribed appropriately
- Assessment of patient's well-being
- Documentation of advance directives

Advance care planning is another key component of quality care [39]. Guidelines recommend that patients with a prognosis of less than 1 year have a discussion on end-of-life preferences [40]. Additional quality guidelines with respect to goals and communication are available [39].

In a secondary analysis of the Temel study, Greer et al. found integration of palliative care into usual oncologic management reduced the administration of chemotherapy within 60 days of death by 0.47 (95 % CI: 0.23–0.99) [11, 38]. There was no difference in the number of rounds of chemotherapy, leading authors to conclude there was better timing of chemotherapy in the palliative care group [38]. Patients receiving a palliative intervention were twice as likely to be referred to hospice care for greater than 7 days prior to death and had a longer median interval between last dose of chemotherapy and death (64 days vs. 41 days) [38].

5.10.2 Life Expectancy and Prognostication

Approximately 80 % of patients want to know prognosis [41, 42]. A great majority (>95 %) with metastatic cancer would like to know treatment options and side

effects [42]. Among 126 patients with incurable cancer, 98 % reported they would like their oncologist to "be realistic about my likely future" [43]. The first of six key elements on individualized care for patients with advanced cancer includes the recommendation that "Patients should be well informed about their prognosis and treatment options…" [44]. They should be informed about the possibility of cure, the response rates of treatments, and effect of treatment on both survival and quality of life [18]. Good communication about prognosis is critical, because the degree of understanding is strongly linked to the treatment choices the patient makes [38, 44]. Murphy showed that if the overall life expectancy was less than 1 year, only 5 % of patients would want CPR after knowing accurate information about outcomes [45]. Despite guidelines recommending advance care planning, discussion of prognosis, and honest communication about options, 4074 physicians surveyed on a hypothetical patient with 4–6 months life expectancy showed that only 65 % would discuss prognosis, 44 % would discuss code status, and 26 % would discuss hospice [46]. Many healthcare providers hesitate, or are unable, to provide accurate prognostic information [47]. Common misconceptions include the belief that it will make people depressed or hopeless, that introduction of hospice or palliative care may reduce length of survival, and that prognostication is inaccurate or inappropriate [40]. Multiple studies have shown that physicians overestimate prognosis and are often grossly optimistic when discussing with patients. Christakis illustrated that physicians overestimate by a factor of 5 [48]. When it comes to prognosis, there are three common strategies that have been described among oncologists: realism, avoidance, and optimism, with each having their own unintended consequences [48, 49]. It has been shown in studies that physician's prognostication is skewed by conscious and unconscious optimism, which will impact a patient's decision regarding treatment options. In truth, this can be helpful in maintaining a patient's hope, and patients indeed prefer hopeful physicians. But this can also lead to more aggressive and futile life-sustaining therapies which take away time for the patient to spend with love ones, time for financial planning, and, in general, time to work toward closure [49]. It will also delay hospice referral, which can greatly impact their quality of life toward end of life. It was not that long ago, about 40 years ago, that a physician would not tell patients their prognosis; however this way of practice compromised patient's autonomy. Thus this practice is out of favor, but surprisingly when physicians were studied, still many preferred nondisclosure to frank disclosure. This could possibly be due to their own inability to formulate reliable prognoses [48]. Also when a physician has realistic prognostic discussions with a patient, they can come off as uncaring and unempathetic. Furthermore, about 20 % of patients do not want to know their prognosis [41, 42].

The two key factors when predicting prognostication is performance status and clinical symptoms. Multiple performance status metrics have been developed to quantify performance status. The three most commonly used are Karnofsky performance status (KPS), Eastern Cooperative Oncology Group (ECOG) system, and Palliative Performance Scale (PPS). In the palliative care setting, it has been proposed that a better way to predict prognosis is to ask "Would I be surprised if my patient died in the next year?" This has been promulgated by palliative care physician, Dr. Joanne Lynn, as a simple way of screening for need for palliative care [50]. This method was validated among 231 Italian general practitioners whose patients

had advanced (stage IV) cancer [51]. The question demonstrated significant correlation with 1-year survival and had a sensitivity of 69 %, specificity of 84 %, positive predictive value of 84 %, and negative predictive value of 69 % [51]. Vigano showed that after performance status, certain clinical signs and symptoms were associated with patient's survival [52]. These include dyspnea, dysphagia, weight loss, xerostomia, anorexia, and cognitive impairment [52]. An integrated model of these two key factors is the Palliative Prognostic Index (PPI) [53]. This study, which predicted a 6-week survival chance with a sensitivity of 62 % and specificity of 86 %, showed that PPI can be used to predict prognosis for patients with advanced cancer [54].

5.11 Communication in Oncology

Several studies have indicated that discrete skills can be taught and learned. While there will always be some clinicians who have a natural ability with their charisma or overall demeanor to relate with patients quickly and succeed at communication, any provider can improve with coaching and practice of techniques designed to break down the process into concrete steps [55]. Incorporating these methods can enhance the clinicians' relationships with patients and their family members, improve quality of cancer care, and even reduce stress and burnout among providers [56]. A recent Cochrane review found that communication skills training in cancer is very effective in that it improves clinician empathy, use of open-ended questions, and assessment of psychosocial needs [57].

A 2013 study in the *Journal of Oncology Practice* analyzed oncologists' strategies and barriers to effective communication about the end of life. The findings shed light on useful tactics clinicians can employ [58]. The majority of the oncologists recognized that goals of care discussions were necessary to ensure the welfare of their patients and that it was a part of their job [58]. The study pointed out the need to have these conversations early and frequently because patients and their families are not able to absorb this information at the initial discussion [58].

5.12 Breaking Bad News

Delivering bad news is one of the most challenging aspects of delivering cancer care, and there are a number of methods providers can use to help patients get the information needed in the most emotionally aware and sensitive manner. One technique that is often employed is the "Ask–Tell–Ask" method developed by Oncotalk, which is a program composed of multiple communication modules designed to improve the skills of the practitioners [59]. The "Ask–Tell–Ask" method involves the clinician asking the patient of their understanding of the topic being discussed by utilizing a prompt such as "Can you tell me what your understanding of your disease is so we can make sure we are both on the same page?" This process of asking the patient for their understanding can help develop a therapeutic alliance with the provider and patient, demonstrates to the patient that their clinician is willing to

listen to them, and can help with directing the flow of a conversation. During the next step, the clinician tells the patient and their family members the information in plain and understandable language. Breaking down the information into layman's language that does not overwhelm the patient is essential. In the last step, the clinician verifies with the patient if they understood the information provided. Asking the patient to teach back the information to the provider can also cement awareness that the patient and clinician have the same level of understanding. This time also allows the patient and family to ask any additional questions they may have.

5.12.1 SPIKES Protocol

The SPIKES protocol was developed by Dr. Robert Buckman [60]. During the first three steps, in a comfortable environment, the clinician should prepare to share the information with the patient. It is important to start by assessing the patient and family. Patients all process information differently and inquiring what the patient would like to know and how they would like to get that information is essential. Some patients are very detail oriented and prefer to have every statistic available, while others prefer a more simplistic "big-picture" approach when it comes to discussing treatment options or goals of care. Furthermore, recognizing if a patient prefers to obtain their information through written materials is key, as oftentimes patients are not able to fully retain what is being told to them when receiving bad news for the first time. During the last three steps, clinicians should try to deliver the news simply, succinctly, and without using medical jargon. It is important for the provider to stop talking after the facts have been stated to allow time for the patient's reactions. After responding to patient and family's concerns, the provider should arrange for follow-up. It can take multiple visits for a patient and family to understand the gravity of their medical illness. Providers need to explicitly tell patients and family that repetition is often necessary and expected and that the provider is ready to answer any questions at subsequent visits. Often patients are not able to formulate all of their questions at the initial visit [60].

- **S**et up the interview
- **P**erception: assess what the patient knows
- **I**nvitation to ask how much they want to know
- **K**nowledge giving regarding medical facts
- Respond to patient and family **E**motions
- **S**trategy and summary including follow up

5.13 GOOD

Similar to the SPIKES+ algorithm for breaking bad news, the GOOD acronym described by palliative care physician Dr. James Hallenbeck in his book *Palliative Care Perspectives* is a useful tool to utilize when having goals of care discussions

with patients and their families [61]. Understanding not only the big-picture goals of the patient but also the goals of others will help the oncologist determine how to frame the discussion. Patients and families may be confused by the question of their goals because they are not used to actively participating in their care. Even most clinicians are not used to asking patients and families up front about goals of care, and therefore patients and families can also be surprised by this question. Figuring out what people fear or wish to avoid in regard to cancer treatment is helpful but, unfortunately, often overlooked.

5.14 "I Want Everything"

A common and difficult scenario for oncologists to deal with is how to discuss treatment preferences with patients who want "everything." In these situations, it is important to determine what "everything" means to the patient [62]. For example, "everything" does not mean that the family and patient want inappropriate and invasive tests with life-prolonging treatment that have a high burden and small chance of benefit. "Everything" can mean only treatments where the benefits outweigh the suffering. Dr. Timothy Quill wrote about four helpful tips to utilize in such situations: (1) try to understand what "everything" means in a cognitive, spiritual, emotional, and familial context, (2) propose a philosophy of treatment that correlates with the patient's values/priorities and with the physician's own assessment of the patient's medical condition and prognosis, (3) recommend a plan of treatment that coincides with the patient's treatment philosophy, and (4) support emotional responses by reinforcing one's commitment to care for the patient regardless of what the future holds [62].

5.15 The Last Hours of Life

Nearly all clinicians will participate in the care of dying patients and their families during some point in their careers. Most patients (90 %) die after a long period of chronic illness and gradual decline resulting in a terminal dying phase. Only 10 % of patients die in an unexpected manner. During the last hours of life, most patients will require around-the-clock skilled care, and such care can be delivered in any setting as long as caregivers are adequately supported throughout the process and have access to the medications, equipment, and supplies needed to provide care for their loved one. Caregivers need to be able to respond to sudden and unexpected changes in the dying patient, and if the patient is at home, they need to be counseled on appropriate interventions to take so unnecessary hospitalizations can be avoided. While it is difficult to give families or caregivers a specific idea of how long the patient might live, they should always be informed about the inherent unpredictability of death and the variety of physiological changes that occur when someone is actively dying.

5.15.1 Palliative Sedation

For refractory delirium and symptom control in actively dying patients with hours or days to live, the NCCN recommends consideration of palliative sedation in consultation with a palliative care specialist. Palliative sedation is the use of medications to induce decreased or absent awareness in order to relieve otherwise intractable suffering at the end of life [63]. Palliative sedation can be used when traditional opioid-based therapies are either inadequate to control suffering or cause unacceptable adverse effects and can also be used to treat delirium, pain, dyspnea, nausea, or other physical symptoms of an actively dying patient [64]. Palliative medicine teams should be involved when palliative sedation is being considered, and it can be appropriate to consult with other experienced colleagues, ethics consultants, and legal departments as needed for advisement when clinical circumstances are unique, such as lack of consensus between staff and family members about the use of palliative sedation. It may be helpful to have other disciplines such as chaplaincy, psychiatry, social work, and anesthesiology teams involved for further assistance as required. Families should be aware that these options exist if symptom control measures continue to fail to help relieve their loved one's suffering.

5.15.2 Physician-Assisted Suicide

Cancer patients who are depressed are more likely to make serious inquiries about physician-assisted suicide (PAS) or euthanasia. Patients may fear future suffering, loss of control, indignity, or being a burden for their loved ones. Euthanasia is defined as "the act of bringing about the death of a hopelessly ill and suffering person in a relatively quick and painless way for reasons of mercy." Physician-assisted suicide is defined as "the act of a physician in providing the means for a patient to hasten his or her death." Although both may have similar goals, physician-assisted suicide and euthanasia fundamentally differ in whether or not the physician participates in the ultimate action that finally ends life. In PAS, the patient performs the act, but the clinician provides the necessary means and information. In euthanasia, the intervention that results in death is performed by the physician.

When a clinician is approached by a patient requesting PAS, the provider should see it as the first expression of unrelieved suffering. Patients have different values, needs, and rationales for making such requests, and it is essential for the physician to clarify the request and explore the person's current suffering and fears while trying to understand the type of request that is being made. The NCCN recommends that a request for hastened death should immediately intensify palliative care, and patients who are not under the care of a palliative care physician should be promptly referred. Determining the underlying causes for the request is important so that the provider may focus on appropriate psychiatric consultation to help treat and diagnose reversible causes of psychological suffering. Depression is often underdiagnosed and thus undertreated in this population. Therefore, it can be a frequent motivator for PAS requests. It is important for the clinician to affirm commitment to

care for the patient and help identify alternatives to PAS after discussion with the family, such as withdrawal of life-sustaining treatment, voluntary cessation of eating or drinking, and palliative sedation. Palliative sedation can be an ethical option for patients within the last hours to days of life who have refractory symptoms and where induction and maintenance of sedation can help when all other available and reasonable therapies have been tried unsuccessfully.

A request for PAS from a patient may be one of the most demanding situations a physician will face. Since requests for hastened death have considerable personal, ethical, and legal ramifications, physicians should seek the support and input of at least one trusted colleague or adviser who may be a mentor, peer, interdisciplinary team member involved in the patient's care, or an ethics consultant. Although PAS is legal under specific circumstances in the states of Oregon, Montana, and Washington, euthanasia is illegal in the United States, and clinicians need to be aware of the legalities of PAS, any pending legislation in their local area, and the institutional guidelines and regulations of where they practice [65].

5.16 Summary

Palliative care is a philosophy of care with the goal of improving quality of life for patients and their families. All physicians practice palliative medicine to some degree. This primary palliative care including communication skills can be acquired and there are various methods to assist in improving this skillset. In addition, certain circumstances may arise with individual patients in which specialty-level palliative medicine is consulted. This may be necessary for complex symptom management including palliative sedation. Also, there may be complex communication that may be necessary. Hospice care is a component of palliative care for patients at the end of life. Co-management between oncology and palliative care is the standard of care for cancer patients.

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Survivorship Care Planning

6

Darcy Burbage

6.1 The Problem

There are over 14 million cancer survivors in the United States, a number that is expected to grow exponentially due to an aging population and improved methods for early detection and treatment [1]. The term "cancer survivor" has evolved over the years. The National Coalition for Cancer Survivorship (NCCS) had originally defined the survival period as the time period from diagnosis through the balance of life, but has recently expanded its definition to include family, friends, and caregivers [2]. In the pivotal Institute of Medicine (IOM) report "From Cancer Patient to Cancer Survivor: Lost in Transition," the importance of addressing the ongoing physical and psychosocial challenges of cancer survivors was emphasized to encourage the multidisciplinary approach to survivorship as a distinct phase of the cancer continuum [3]. The report recommended that essential components of survivorship care include prevention and detection of new cancers, surveillance for recurrence, genetic evaluation, addressing the physical and psychosocial consequences of cancer and its treatment, and the coordination of care between specialists and primary care providers (PCPs).

The American Society of Clinical Oncology (ASCO) has described the stages of survivorship as acute, extended, and permanent [4]. The acute phase describes the time frame from diagnosis through initial treatment. The extended time frame is the period immediately after treatment is completed. The permanent phase is described as a longer time frame usually in years [4]. Each of these time frames presents its own set of unique challenges as survivors continue to recover from

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the late effects of treatment, begin to discover their new "normal," and transition to less frequent visits with their healthcare providers. Much of what is evolving in adult cancer survivorship care can be learned from pediatric cancer research [5, 6]. Evidence-based surveillance and follow-up guidelines for pediatric cancer survivors were first published in 2004 by the Children's Oncology Group [7]. Although evidence-based guidelines exist for some common adult cancers such as breast and colon cancer, most others are lacking. One barrier to providing standardized care to adult cancer survivors is the variability between survivors with the same type of cancer who may also present with comorbidities along with the use of personalized treatment plans [6].

In addition to the lack of guidelines for survivorship care planning, a gap exists in the provision of care provided to survivors leading to a potential deficit in the access to high-quality survivorship care. Howell et al. [8] reviewed models of survivorship care in an effort to evaluate the efficacy of current survivorship planning. The authors concluded that further research is needed on how to best structure survivorship care. This lends support to the theory that there is not a "one-size-fits-all" approach to survivorship program planning. Regardless of the practice setting, all models of survivorship care share a common goal, improving the quality of care provided to cancer survivors [9–11]. While the definition of a cancer survivor is broad, unless otherwise specified in this chapter, a survivor will be defined as an adult with a history of cancer. This chapter will examine the various models utilized to provide survivorship care to adults, discuss implementing survivorship treatment summaries into clinical practice, review surveillance guidelines and health promotion strategies, and conclude with considerations for the healthcare provider to help improve the care provided to cancer survivors in the future.

6.2 Evidence

Cancer survivors often experience physical and psychosocial long-term and late effects after treatment ends [12]. Long-term effects include fatigue, peripheral neuropathy, pain, and cognitive changes that can occur during treatment and continue well beyond the end of treatment [13]. Late effects of therapy, such as cardiac dysfunction, pulmonary fibrosis, lymphedema, and secondary malignancies, can occur as late as 20 years after treatment [13]. Multiple other physical effects of cancer treatment that may appear are related to the disease-specific treatment regimen provided in addition to the individual's underlying comorbidities. With the discovery of newer chemotherapeutic agents, unanticipated side effects may also emerge [5].

In addition to physical challenges, research has shown that survivors have an increased risk for psychosocial distress as a result of a cancer diagnosis. Studies have shown an increased risk of psychosocial distress in survivors who are younger, those with inadequate socioeconomic resources, limited access to care, communication barriers, underlying comorbid illness, and a history of psychiatric disorders [14, 15]. Psychosocial adjustments to life after cancer can include difficulty concentrating, anxiety, insomnia, depression, and post-traumatic stress disorder [14, 15].

Vachon [14] reported that even though approximately one-third of individuals with cancer experience some psychosocial distress, only about 10 % of these individuals receive therapy to address it. In a survey of over 3000 survivors, 98 % of respondents indicated that they experienced continued concerns as a result of cancer treatment [15]. Of these same respondents, 75 % indicated a fear of recurrence, followed by depression/sadness (65 %), while 53 % reported low-energy, sleep disturbance, and difficulty concentrating. Ness et al. [12] identified the following top five concerns of cancer survivors as fear of recurrence, fatigue, living with uncertainty, managing stress, and sleep disturbance. Social isolation, intimacy issues, spiritual distress, alterations in body image, and sexuality concerns were also identified by survivors as causes of distress [12, 16].

The literature is replete with articles that address the process for implementing survivorship care planning into clinical practice [6, 8, 11, 17–19]. Multiple models have been proposed for survivorship programs as there is no "one-size-fits-all" model of delivering survivorship care, and these programs are still evolving. Adult follow-up programs traditionally focus on a medical model. In this model, survivors are usually seen by a mid-level provider of their primary oncology team who performs a physical examination and assesses survivors for long-term and late effects of treatment. Referrals for additional services are made by the provider to programs within the facility or to resources in their community [9]. A consultative model employs a one-time comprehensive visit for survivors at the end of treatment which includes a review of therapy received as well as recommendations for health promotion and surveillance [9, 17]. Additional consultations with ancillary support services such as rehabilitation and psychosocial counseling can be recommended, and the ongoing care continues to be provided by the survivor's oncology team [9, 17]. Earle and Ganz [20] reported that several hours are required outside of the survivorship visit to adequately prepare for this appointment.

In a multidisciplinary clinic model, multiple providers are available during the survivor's scheduled appointment time. This type of model was the first developed and is still in use today in pediatric survivorship programs [9]. This model is usually costly, resource intensive, and may not be feasible for adult survivorship programs.

In an integrated care model, survivors remain under the care of their primary oncology team; however, care is usually provided by a mid-level provider in the same practice. Care may then be transitioned to the survivor's primary care provider at a specific interval [9]. In order for the transition to primary care to be successful, primary care providers must be given the necessary information to provide ongoing surveillance for long-term and late effects of treatment. With each of the models noted above, however, survivors will need an additional posttreatment appointment to review long-term and late effects of treatment, health promotion, and surveillance recommendations.

In some practice settings, oncology nurse navigators are being utilized to provide survivorship counseling. In this model, navigators present evidence-based information on potential long-term and late effects of treatment and educate patients on the resources available to them and their families during this phase of the cancer continuum. In this author's clinical experience, a survivorship nurse navigator is

embedded in the department of radiation oncology and meets with survivors during the last week of treatment and again at their initial follow-up appointment to assess for unmet physical and psychosocial needs, making referrals to resources based on assessment results. In addition, the survivorship nurse navigator prepares the survivorship treatment summary and care plan and reviews it individually with each survivor [21].

When developing a survivorship program, it is important to take into account the individual practice settings along with available resources (financial as well as personnel), the survivor population, and optimal time for implementation [9, 20, 22]. Maintaining flexibility and open communication are also essential components of the program development process.

Trotter et al. [23] implemented a multidisciplinary clinic for breast cancer survivors that utilized a group visit medical model. In this pilot program, six breast cancer survivors who were at least 3 years beyond diagnosis and without evidence of metastatic disease were eligible to participate. A nurse practitioner facilitated the group with an oncology-certified licensed clinical social worker, dietitian, and physical therapist with lymphedema certification, who were available for brief consultations free of charge for each survivor as requested. At the time of publication, the cost-benefit analysis for this type of program was still being determined [23].

Mayer et al. [18] explored breast cancer survivors' preferences of providing survivorship care. Survivors completed a questionnaire to evaluate their comfort level with follow-up care provided by their PCP, medical oncologist, radiation oncologist, surgeon, nurse practitioner (NP), and a virtual visit. Patients were then asked how visiting each provider would affect their stress, cancer-related worry, and survival outcomes. The greatest decreases in stress and cancer-related worry were found by visiting the medical oncologist followed by statistically equivalent results noted by visiting the radiation oncologist, surgeon, NP, or PCP [18]. When questioned about the effect of follow-up visits on improving survival outcomes, once again, a large percentage of survivors indicated that visiting the medical oncologist was likely to improve their survival outcomes. In each response, the virtual visit was ranked last for decreasing stress and cancer-related worry and the least likely to improve survival.

According to Grunfield and Earle [24] after cancer treatment is completed, some patients expect that their oncologist will become their primary care provider, which can lead to inconsistencies and confusion for the patient, oncologist, and primary care provider. Although some oncologists are willing to take on this role, the majority are not [24]. The reverse is also true as some primary care providers are willing to take responsibility for providing survivorship care to their patients while others are not. Survivorship care includes not only surveillance for recurrence; it also includes the management of long-term and late effects of treatment such as the increased risk of cardiac dysfunction along with continued neuropathy from certain chemotherapeutic agents. Psychosocial issues such as fear of recurrence, depression, and anxiety may occur at any point in the survivorship continuum. The National Comprehensive Cancer Network (NCCN) along with the American

Society of Clinical Oncology (ASCO) is beginning to develop evidence-based survivorship guidelines to address these issues.

The need for survivorship education and care planning also extends to other healthcare providers. In one study, Lester et al. [25] surveyed over 200 oncology nurses at one comprehensive cancer center in the Midwest and found that gaps exist in the knowledge of survivorship care planning. Even though results from this study cannot be generalized to other practice settings due its small sample size, the findings warrant further research and increased education to oncology nurses. The Oncology Nursing Society (ONS) provides conferences, online courses, books, peer-reviewed journals, and a survivorship, quality of life, and rehabilitation special interest group to help educate nurses on the unique challenges faced by cancer survivors.

Regardless of the type of survivorship model or program that is implemented, the importance of communication and coordination of care between oncologists and primary care providers cannot be understated [24]. One mechanism to assist in the communication and coordination of care is the survivorship treatment summary and care plan.

6.3 Ongoing Research

One of the recommendations made in the IOM report to improve communication between oncologists and primary care providers is the utilization of a survivorship treatment summary and care plan [3]. Because of the IOM's recommendation, the American College of Surgeon's Commission on Cancer standards released in 2012 also called for the implementation of a survivorship care plan (SCP) by accredited programs by 2015 [26]. Standard 3.3 of the Commission on Cancer (CoC) requires that:

- A survivorship care plan is prepared by the principal provider(s) who coordinated the oncology treatment for the patient with input from the patient's other providers.
- The survivorship care plan is given to the patient on completion of treatment.
- The written or electronic survivorship care plan contains a record of care received, important disease characteristics, and a follow-up care plan incorporating available and recognized evidence-based standards of care, when available. The minimum care plan standards are identified in the Fact Sheet: Cancer Survivorship Care Planning, from the IOM.

Although the Commission on Cancer [26] sets the survivorship care plan as a standard and several cancer advocacy groups recommend that survivors receive a summary of the treatment they received, implementation has been inconsistent [27]. Reasons cited for this inconsistency include the length of time needed to complete the treatment summary, the inability of current electronic health record systems to streamline the process, and a lack of reimbursement [22, 27]. In addition to these

concerns, multiple templates have been developed by professional and patient advocacy organizations as well as those created by individual institutions to address recommendations from the IOM [22, 28]. Despite some commonalities, the content and length of the templates vary. There is also limited evidence documenting their effectiveness in improving clinical outcomes and compliance with follow-up recommendations [22]. Salz et al. [29] surveyed principal investigators at 14 NCI Community Cancer Centers Program (NCCCP) hospitals regarding the use of SCPs: specifically, the use and perceived value of SCPs, along with barriers to its implementation. Although 87–89 % of providers believed it was important for PCPs to receive the information, only 58–65 % believed it was important for survivors to receive this information, while fewer than half actually provided a SCP to their survivors [29]. In addition, a lack of personnel and time were also identified as barriers to implementation. However, among those utilizing an SCP, the providers found the use of a template to be very helpful. Since the survivorship care plan implementation standard is not required until 2015, the literature is limited to a few randomized control studies evaluating the survivorship care plan for its usefulness and effectiveness for survivors and healthcare providers. In one study of breast and colorectal survivors, survivors indicated that although the survivorship care plan was helpful in understanding the care they received, confusion remained as to which provider was responsible for the coordination of their care [30]. In another study by Grunfield et al. [31], breast cancer survivors who received a survivorship care plan experienced no benefit in quality of life, distress, or satisfaction as compared to survivors who received a traditional discharge visit. Mayer, Gerstel, Leak, and Smith [28] conducted focus groups with both survivors and primary care providers to evaluate their experiences and preferences in the content, format, and the delivery of a survivorship care plan. Results revealed that both survivors and PCPs found the SCP helpful. However, the survivors wanted information earlier on in their diagnosis and treatment in addition to surveillance and health promotion information after completing treatment, while the providers wanted a condensed version of the SCP at the end of treatment with an overview of treatment received, symptoms of recurrence, surveillance information, and responsible clinician [28].

Ashing-Giwa et al. [32] studied SCPs in African-American breast cancer survivors. It is a known statistic that African-American breast cancer survivors tend to experience greater morbidity and overall mortality as compared to Caucasian breast cancer survivors [1]. In this study, three structured focus groups were conducted to evaluate current knowledge of SCPs, review components recommended by the IOM, provide feedback, and draft a culturally relevant SCP template. Participants in this study raised concerns that the higher morbidity and mortality in African-American breast cancer survivors may be a result of more comorbidities and inadequate surveillance. Results from this study suggested that African-American breast cancer survivors wanted the SCP to be inclusive of other medical comorbidities that may have an impact on their overall survival [32]. This study provides an important and relevant aspect in providing individualized and culturally competent care to survivors. In another study, Pedro and Schmiege [33] found that survivors in rural areas reported lower social function and increased financial challenges and number

of symptoms and concluded that health-related quality of life outcomes may be diminished posttreatment. Additional challenges in the rural setting include access to care, including transportation issues and health literacy [11]. Just as there is not a "one-size-fits-all" approach to survivorship models of care, there also needs to be individualization of the survivorship care plan itself to meet the needs of survivors in diverse populations.

As important as the survivorship care plan can be in its ability to communicate treatment received, recommended surveillance and health promotion guidelines, without adequate explanation to the survivor and other healthcare providers involved in their care, it only accomplishes half of its goal. Survivorship care planning is more than a piece of paper; it is a process that starts at diagnosis and continues throughout the survivors' journey and transition into survivorship. A collaborative project between the American Cancer Society and the George Washington Cancer Center established the National Cancer Survivorship Resource Center, which has developed the Cancer Survivorship E-Learning series. This program sponsors free continuing education programs to educate healthcare providers on how to better care for survivors in their practice settings.

In addition to the physical challenges that survivors face, many survivors also experience psychosocial distress throughout their survivorship journey. Although not specifically addressed in this chapter, screening for distress is another important aspect of survivorship care planning that must be considered and has recently been added to the Commission on Cancer accreditation requirements [26]. As difficult as it is to predict which survivors will develop physical late effects of treatment, it can be even more difficult to foresee the psychosocial late effects of treatment. In some cases, psychosocial concerns may increase the physical effects of cancer such as pain, fatigue, insomnia, and cognitive changes. Fear of recurrence is the greatest concern expressed by survivors followed by fatigue [12, 15].

Multiple reliable and valid resources are available to assist the healthcare provider in assessing survivors for psychosocial distress, such as the Distress Thermometer developed by the National Comprehensive Cancer Network, the Patient Health Questionnaire (PHQ), the Psychosocial Screen for Cancer, and the Brief Symptom Inventory 18 to name a few. Although accreditation standards and tools exist to support the healthcare provider, barriers remain in the implementation process. Time, personnel, available psychosocial resources, multiple electronic health records, and the belief that survivors do not want to discuss distress have been identified as barriers [34]. In addition, survivors have identified barriers such as transportation issues, coping with ongoing side effects, and the stigma associated with seeking psychosocial support as reasons for not obtaining assistance [35].

In an article by Forsythe et al. [36], medical oncologists and PCPs were surveyed to determine who provides psychosocial care to breast and colon cancer survivors. In both groups, the medical oncologists and PCPs endorsed their own groups as the resource for not only providing psychosocial care but also for health promotion and the management of physical symptoms. The authors concluded that the results were inconsistent with survivor's perception of unmet needs and lend support to the shared approach to survivorship care between the PCPs and medical oncologists [36].

Petty and Lester [37] summarized studies of distress screening in cancer survivors and found that as psychosocial distress increased, so did healthcare expenses. In reality, the inverse was true; that as distress was recognized and treated appropriately, visits to PCPs and specialists decreased. The authors concluded that distress needs to proactively be assessed since the number of long-term survivors is increasing, as well as the number of survivors living with metastatic disease.

In screening survivors for psychosocial distress, it is important to include the needs of the family in the assessment, as the impact of cancer often extends to members of the survivor's supportive network, especially those who have been identified as the primary caregiver. Financial concerns along with changes in relationships can linger well after treatment has ended and can continue if not adequately identified and appropriate interventions implemented. Individual, couples, and/or family counseling can be extremely helpful for the survivor and their support system. In addition, joining a support group can provide opportunities for survivors and caregivers to share their experiences with others and help cope with effects of treatment. Cancer specific as well as in-person and online support groups are available through the Cancer Support Community, the American Cancer Society, and CancerCare and are only a few of the many resources available to assist survivors, caregivers, and their families in managing the psychosocial challenges of a cancer diagnosis.

6.4 Solutions

In an effort to improve survivorship care planning, a shift needs to occur within the healthcare community that helps the survivor transition from active treatment to life after treatment. For some survivors, the treatment phase is relatively short, such as in the case of an early stage melanoma survivor who may require only surgery as compared to survivors with advanced head and neck or breast cancer whose treatment may entail surgery followed by chemotherapy, radiation therapy, and/or other modalities in which recommended therapy may last upward of a year.

While completing active treatment is a source of celebration with certificates being handed out and/or the ceremonial ringing of a bell for others, it is a known fact that a cancer diagnosis has a significant impact on individuals and their support system. As discussed in this chapter and throughout this book, the physical and psychosocial effects of treatment can be long term or occur many years after treatment has been completed. Although it has been almost 30 years since pioneers in the survivorship movement convened in New Mexico and formally articulated the definition of a survivor, healthcare providers are just now beginning to recognize that survivorship is a distinct phase of the cancer continuum [5].

In 2014, both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) began releasing guidelines for survivorship care. Digiulo [38] reported that the ASCO Survivorship Guideline Advisory Group ranked a comprehensive list of issues and selected chemotherapy-induced peripheral neuropathy, fatigue, anxiety, and depression as their top priority in a planned series of survivorship guidelines. The NCCN selected anxiety and

depression, cognitive function, pain, female and male sexual dysfunction, fatigue, sleep disorders, exercise, immunizations, and prevention of infections as their initial topics for survivorship care [39]. Both the ASCO and the NCCN guidelines provide evidence-based recommendations for the assessment, evaluation, and treatment for common sequelae of cancer treatment. Additional topics from both organizations will be addressed in the future [38, 39].

In addition to managing the long-term and late effects of cancer treatment, the survivor will need to be monitored closely for signs of recurrence. Disease-specific and individual recommendations for ongoing surveillance should be addressed as part of the survivorship care planning process and discussed with the survivor throughout the continuum of care. The NCCN along with the ASCO provide evidence-based recommendations for surveillance. As discussed earlier in this chapter, a summary of the treatment received and follow-up plan is essential in coordinating care for the survivor.

Another mechanism to improve the overall health and well-being of the survivor is to assess for ongoing functional limitations and provide opportunities for rehabilitation along with health-promotion strategies to improve overall wellness. Rehabilitation is valuable for survivors throughout the cancer continuum by helping to improve physical strength, mobility, and balance and reduce fatigue, pain, anxiety, and depression [40]. Depending upon the type of cancer and the survivor's comorbidities, rehabilitation may also include speech and swallowing evaluation, management of bladder and bowel dysfunction, stoma care, and use of prosthetics and other assistive devices [40]. More than the ability to perform activities of daily living, cancer rehabilitation assists the survivor to improve their quality of life. Recent research is now encouraging the use of "cancer prehabilitation" which advocates for therapy to occur prior to and during active treatment to help reduce potential functional impairments, thereby improving outcomes and perhaps even reducing healthcare costs [40].

In addition to the physical and in some instances the vocational rehabilitation of survivors, healthcare providers are in a unique position to assist survivors in making positive lifestyle changes. As compared to the general population, cancer survivors are at an increased risk for developing health problems as a result of their cancer treatment [41]. Harding [41] surveyed cancer survivors regarding the prevalence of smoking, alcohol use, physical exercise, and psychosocial distress. Results indicated that respondents continued to smoke at a rate similar to the national average, while levels of physical activity differed among age groups, with the frequency of physical activity declining with age. The pattern of alcohol use indicated that 18 % reported drinking at a risky level, while survivors between the ages of 18 and 40 reported hopelessness (26 %), anxiety (56 %), and sadness (39 %) much or most of the time. The author concluded that healthcare providers should proactively assess for smoking status, physical activity, alcohol use, and psychosocial distress during posttreatment care and provide guidance in adopting healthy lifestyle choices [41].

In a study by Rosales et al. [42], breast cancer survivors reported their top five concerns as weight management (35 %), fatigue (30 %), body image/sexual functioning (27 %), anxiety/fear of recurrence (23 %), and caregiver stress (17 %). At 1

month posttreatment, 80 % of survivors were continuing to work on these identified wellness goals.

In 2012, the American Cancer Society published nutrition and activity guidelines for cancer survivors [43]. To summarize, these guidelines recommend that survivors achieve and maintain a healthy weight, engage in at least 150 min of regular exercise per week (to include strength training at least 2 days a week), and to achieve a diet high in vegetables, fruits, and whole grains. Although not studied in all cancer types, research regarding the impact of cancer recurrence, cancer mortality, and overall mortality has been studied in breast, ovarian, prostate, and colorectal cancer survivors and has demonstrated that physical activity has been associated with improved survival and decreased disease recurrence. For more information on nutrition and the cancer survivor, please see Chap. 12.

In addition to smoking cessation, healthy eating, regular exercise, and reducing alcohol intake, managing stress is another important aspect of health promotion behaviors for the cancer survivor. Integrative therapies such as yoga have also been examined in breast cancer survivors. Although more research is needed, a recent study has demonstrated that yoga can improve psychological health outcomes, such as anxiety, fatigue, depression, and distress [43, 44]. Mind/body techniques such as meditation, prayer, guided imagery, art therapy, and energy therapies such as Reiki and Qigong have also been shown to be effective in reducing anxiety [45]. Many survivors also find that keeping a journal, reaching out for spiritual support, volunteering, and reevaluating priorities can enhance their quality of life.

6.5 Future Directions

As the number of adult and pediatric cancer survivors continues to increase, so does the need for coordinated survivorship care planning. Providing care to survivors will be a challenge for institutions, private practices, and community agencies, as multiple healthcare providers will need to be educated on the expanding demand for survivorship services to provide quality care to this unique population. Economou et al. [46] examined the role of oncology advanced practice nurses (APNs) to meet this challenge. The authors concluded that based on their advanced education and clinical expertise, oncology APNs can provide cost-effective care and can contribute to improved patient outcomes in cancer survivors.

Cancer survivorship is not a linear process, but a journey that begins at diagnosis and hopefully continues for many years. Regardless of the practice setting or role, healthcare providers should provide ongoing education to survivors on their diagnosis, potential treatment-related effects (both physical and psychosocial), and symptoms to report with the ultimate goal of empowering survivors to advocate for themselves. As we work toward evidence-based clinical outcomes, ongoing research should focus on the impact that various survivorship models have on survivor outcomes while including the medically underserved and those from diverse cultural backgrounds, the effectiveness of survivorship treatment summaries, and follow-up

care plans on adherence to surveillance guidelines and address the impact that survivorship care planning has on health promotion.

In addition to those living with extended disease-free survival, there is also a group of survivors who are living with stable metastatic disease. Although not addressed in this chapter, this is another evolving aspect of survivorship care planning that needs attention, as this population of survivors has their own distinct set of challenges and provides a unique opportunity for healthcare providers.

Survivorship is a developing concept with little clear guidance regarding the optimum time to deliver survivorship care and who is ultimately responsible for providing care to survivors, as the cancer experience is different for each individual. In some instances, survivors themselves don't like the word survivor or don't consider themselves a survivor, making it difficult for healthcare providers to determine the optimal time to provide survivorship care planning or to standardize survivorship care [5]. Barriers in providing survivorship care planning are many and include a lack of funding for personnel, patient access, a lack of reimbursement specific for survivorship services, and time [6]. During the writing of this chapter, numerous articles have been published on various aspects of survivorship care planning, lending support to the idea that survivorship care planning continues to evolve. Providing ongoing educational opportunities for healthcare providers will be critical as we strive toward improved patient care outcomes.

Ongoing communication between all healthcare providers involved in the care of cancer survivors will continue to be essential in providing seamless and coordinated care. As the process for completing and delivering survivorship treatment summaries and care plans continues to evolve, including the survivor in discussions for their ongoing surveillance will be paramount to assuring the delivery of individualized survivorship care.

Finally, both professional and patient advocacy organizations need to continue to lobby policy makers to increase funding for survivorship care planning and to include survivor-specific education, access to quality survivorship care, the development of evidence-based clinical practice guidelines, clinical trials that specifically address long-term and late physical and psychosocial effects of treatment, survivorship education, training opportunities for PCPs and APNs involved in the care of survivors, and a determination of specific coding and reimbursement mandates for healthcare providers [6].

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Fundamentals of Cancer Pain Management

7

Thomas J. Smith and Joe O'Neil

7.1 The Problem

Pain is the most common and most feared symptom among cancer patients. At least 75 % of cancer patients will have significant pain, and the pain usually increases as the disease progresses and the end of life nears. While fatigue may be more common, and delirium and dyspnea near the end of life may be more bothersome to caregivers [1], pain is a common denominator in all of our conversations with cancer patients and their families. A meta-analysis of the prevalence of pain in cancer patients calculated rates of 33 % in patients after curative treatment, 59 % in patients undergoing cancer treatment, 64 % in patients with advanced/metastatic/terminal cancer, and an overall rate of 53 % [2].

One would think that in the developed world, after 50 years of opioid availability, 30 years of Continuing Medical Education (CME) about pain for healthcare practitioners, and 10 years of promulgation of "Pain as the 5th Vital Sign," that pain would be a solved problem. But it is not. Fisch and colleagues followed 3, 123 ambulatory cancer patients (breast, prostate, colon/rectum, lung) and found that 67 % had pain at their initial visit and 33 % were receiving inadequate analgesics.

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This inadequate analgesic prescribing persisted at follow-up visits and did not improve. Worse, minority patients had double the odds of inadequate prescribing [3]. Surprisingly, the figures have not changed appreciably from 18 years prior [4], even in a prospective study with interested participants who knew they were under observation.

While this situation is bad in the developed world [5], it is even worse in developing economies. Cancer is quickly becoming as common in the rest of the world [6] as in the developed – mostly Western – world. As life expectancy increases, and with adoption of the Western diet, cigarettes, industrialization, and the spread of cancer-causing viruses like Hepatitis C, cancer promises to be a leading global health problem far into the future: the World Health Organization estimates that annual cancer incidence will rise from 14 million in 2012 to 22 million within the next two decades [7].

The pain associated with these illnesses, magnified by the lack of opioid availability in many parts of the world, will grow as well. The World Health Organization (WHO) estimates that 80 % of the world's population does not have access to morphine for pain relief [8].

Curing cancer is often a necessary, but rarely a sufficient, step to relieve patients of their pain, because in addition to pain caused by the tumor, for many, pain arising from the treatment itself (radiation, chemotherapy, surgery) is significant and must be also addressed [9]. In an editorial in *the Journal of Clinical Oncology*, Martin Stockler called for "ensuring that every consultation includes the patient's rating of pain, that the oncologist pays attention to the answer, and that there is an agreed-upon plan to increase analgesia when it is inadequate" [10].

Universal adherence to this exhortation would certainly be helpful as far as it goes. The management of pain in cancer, even for the experienced clinician, is more nuanced and complicated than it may initially appear. Practitioners need to have a workable taxonomy of pain so that the therapies can be tailored appropriately. For example, "incident pain," which occurs when a limb is moved, requires a different approach than neuropathic pain occurring in the same location or visceral pain that may be present at the same time in another location.

To further complicate matters, it must be recognized that there are many variables that contribute to a pain symptom and, hence, more than one approach to treating pain is often needed. Dame Cicely Saunders pioneered the "Total Pain" concept that chronic pain arises from multiple dimensions of human experience – social, practical, spiritual, psychological, and physical [11]. This paradigm underpins the contemporary hospice and palliative care approach to pain and is the reason that palliative practice adopts a multidisciplinary approach to symptom management that can attend to any and all elements of a patient's suffering. It is important to remember, therefore, that when faced with difficult cancer pain, the primary provider and the patient will benefit by seeking help from a range of disciplines including, but not limited to, pastoral care and psychology. Even the best care utilizing the most advanced techniques and following the most current and evidence-based guidelines fails to deliver adequate pain relief to 10–20 % of patients [12].

7.2 Evidence

The International Society for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [13]. Acute pain is generally adaptive in that it causes avoidance of injurious situations or promotes healing by fostering immobilization of an injured body part. Chronic pain of the type associated with cancer does not have such adaptive purposes.

7.2.1 Pathophysiology of Pain in Cancer

The sensation of pain has been described as the result of a process "tantamount to an orchestral concert, with each individual instrument contributing a subtle yet important element composing the final product" [14]. Although considerable progress has been made in identifying the various elements involved in cancer pain and in understanding the complex process by which they interact, this field remains one in which novel discoveries have the potential to significantly contribute to mitigation of human suffering.

Pain in cancer is the result of complex interactions between cancer cells themselves, the peripheral and central nervous systems, and the immune system [15].

In this process, cancer cells produce a wide range of substances that mediate or interact with pain receptors (nociceptors). As more is understood about the functioning of these molecules in the transduction process, they have emerged as important targets for novel analgesic interventions [16]. Additionally, peripheral nocireceptors themselves appear to become activated, sensitized, or injured in the presence of certain cancers [17].

Once receptors are stimulated, impulses are transmitted first by afferent A-δ (thinly myelinated) fibers and later by slower (nonmyelinated) C-fibers. These end in cell bodies in the dorsal root or trigeminal ganglion that, in turn and in complex ways, interact with neurons in the central nervous system through cells in the spinal cord. These spinal cells project axons to the contralateral thalamus from which impulses are transmitted to regions of the cortex via somatosensory pathways. Interactions at the cortical level are highly complex involving the somatosensory cortex, frontal cortex, and limbic system.

The observation that perceptions of pain can vary depending upon factors that have no direct relation to nociceptors (anxiety, depression, distraction, etc.) indicates the presence of additional mechanisms that modulate transduction. These include inhibition at the spinal level by non-painful input (the Gate Theory), as well as descending inhibition from midbrain and higher regions that contain high concentrations of opioid receptors.

Visceral pain arising from nociceptors in internal organs is mostly transmitted by unmyelinated C-fibers. Often less well localized and less sharp than somatic pain, visceral pain is triggered by direct irritation from the tumor, distention or contraction of an organ, ischemia, necrosis, or inflammatory mediators.

Neuropathic pain arises from injury to nerve tissue in either the central or peripheral system. It differs from nociceptive pain in two important ways. First, there is no transduction from a nociceptor to a nerve. Rather, the nerve itself generates the pain impulse. Second, nerve damage is more likely than damage to other tissue to result in chronic pain; that is, the pain impulse continues after the insult is gone. The prognosis is, therefore, worse and such pain is less likely to respond to standard opioid or NSAID-based therapy [18]. Neuropathic pain is also complicated by the widely accepted "wind-up" phenomena: repetitive stimulation of the C-fibers leads to biochemical and physical genetic changes in the central nervous system. In fact, the damaged nerves and their undamaged counterparts may both be giving signals of the damaged nerves by crosstalk, reinforcing the pain stimulus [19].

In cancer, such injury often arises as a result of treatment (chemotherapy, surgery, or radiotherapy) but can also be caused by infection, direct action of the tumor, ischemia, or other mechanisms. Unlike somatic or visceral pain, the quality of neuropathic pain is often described as burning or numbing and may be further diagnosed as allodynic (caused by stimuli that do not normally trigger pain) or hyperalgesic (pain perception is much greater than would be expected from a normally painful stimuli). The distinction between nociceptive pain (somatic and visceral) and neuropathic pain is clinically important as different therapeutic approaches are often needed to achieve relief.

7.2.2 Approach to the Cancer Patient in Pain

One of the most significant challenges facing the clinician is to build an objective framework from which to assess and monitor the patient's subjective, or self-reported, experience of pain [20]. Without it, measuring the progression of disease and understanding the impact and efficacy of therapeutic interventions are difficult. Various interview techniques, assessment tools, technologies, and scales have been evaluated and deployed for this purpose. Particularly challenging patients include infants and children, the elderly, and those with mental incapacity or inability to communicate.

The NIH (National Institute of Health) Toolbox of Neurological and Behavioral Function that was developed to provide a set of measures derived from scholarly and expert input to measure various aspects of neurologic function recommends a self-report measure of pain intensity using a 1–10 rating scale [21]. Visual analog or verbal rating scales also have important roles to play. Regardless of what reporting scale is used, it must be impressed upon patients and their families that they must report pain and be an active partner in its management. The clinician should ask about pain frequently and, at a minimum, at every clinical encounter. Understanding and tracking the location, quality, mitigating and exacerbating factors, triggers, and temporal patterns are essential in diagnosing the etiology of, and treatment for, the symptom. Ongoing efforts to develop universal pain classification systems as a means to improve assessment and facilitate research are underway [22].

Physical examination can provide important clues to the etiology of pain, especially if it is neuropathic in origin. It is important always to take a moment and

simply observe the patient. Do they appear comfortable? Are they grimacing or furrowing their brow? What is their respiratory rate? Are they tachypneic? A finding of any of these could indicate the presence of unacknowledged pain. The lack of such finding, however, does not rule out the presence of pain especially if it is chronic in nature. An area of erythema, swelling, or tenderness to palpation can direct attention to a specific etiology and elicitation of hyper- and dys-, or anesthesia in a region can indicate a neuropathic pain problem. Even, however, if the encounter yields no useful information, physical examination is an occasion of appropriate (procedural) touch by the provider. Touch has been suggested to be helpful in communication and, hence, patient satisfaction [23].

7.2.3 Management of Cancer Pain

The World Health Organization (WHO) has, for over 25 years, promulgated a three-step pain management paradigm that has garnered near-universal acceptance as normative for pain management strategies in adults [7]. A separate two-step approach is recommended for children.

The basic WHO approach recognizes three fundamental categories of analgesics – non-opioids (aspirin, acetaminophen, paracetamol, or NSAIDs), "weak" opioids (codeine), and strong opioids (morphine, hydromorphone and others) – and three levels of pain (mild, mild-moderate, and moderate-severe). Mild pain is recommended to be treated with non-opioids, mild-moderate with "weak" opioids +/– a non-opioid, and moderate-severe with strong opioids +/– non-opioids. Adjuvant medications are recommended on an ad hoc basis, and in all cases, the WHO paradigm recommends around-the-clock dosing of analgesics with provision of breakthrough or rescue doses and adaption of regimens based upon individual needs, patient education, and administration via the oral route when possible.

While an essential strategy for pain management and advocacy for increased access to opiates in resource-limited regions of the world, this approach includes several aspects that warrant further consideration in cancer pain. These include the use of low doses of strong opiates for mild-moderate pain (elimination of step 2 on the ladder), clinical implications of long-term use of NSAIDs, validation of various routes of administration pain, addition of a fourth step that recruits surgical and other interventions for severe and intractable pain, and specific recognition of neuropathic pain requiring a different approach [24, 25].

Table 7.1 summarizes the array of approaches to treat cancer pain available to practitioners in the United States.

7.3 Opioids

Opioids are the backbone of most all strategies to control cancer pain. There are three types of opiate receptors in the central and peripheral nervous systems whose role has been well established in pain management. Originally called mu, delta, and kappa, these receptors were renamed MOP, DOP, and KOP, respectively, in 2000 by

Table 7.1 Standard ways of relieving pain

Method	Application	Effectiveness	Comments and references
Opioids	Somatic pain Neuropathic pain Mixed pain		In one underpowered randomized trial, methadone had no more effect than morphine in neuropathic pain
Adjuvant drugs Antidepressants Neuroleptics/seizure medications Steroids	Somatic pain Neuropathic pain Mixed pain		
Bone strengtheners	Bisphosphonates Denosumab	50–70 % of patients report benefit May delay bone pain more than bisphosphonates but substantially more expensive ($2500 or more versus $600)	
Radiation therapy	Bone pain Incident pain (pain on movement of bones, for which opioids are only partially effective, at the cost of oversedation) [26]. A few patients have been treated with opioid switching and "burst" ketamine at 100 mg/day [27]	70 % or more experience pain relief	
Surgery		Very little actual data May be used more for obstruction	
Nerve blocks	Celiac and other plexus blocks Local injections	In general, about a 75 % chance of success, with the ability to repeat in the future if needed	

Table 7.1 (continued)

Method	Application	Effectiveness	Comments and references
Advanced locoregional pain techniques	Spinal cord stimulation Peripheral nerve stimulation Intrathecal infusion Scrambler therapy	Over half of patients experience significant benefit Appears similar to spinal cord stimulation but with no randomized trials Randomized trial shows better pain control, less drug toxicity, and longer survival compared to conventional best pain management One randomized trial and multiple uncontrolled trials show effective relief of pain with minimal side effects	

the International Union of Pharmacology. There is a fourth receptor called the nociceptin receptor or NOP which, although has similar biochemical structures to the classic opioid receptors, does not appear to react to naloxone and, hence, is considered a non-opioid branch of the opioid receptor family [28].

Opioid analgesic drugs are classified by their strength, by the type of action they have on opiate receptors (full opioid receptor agonists, partial agonists, and mixed agonists/antagonist), and by whether they are semisynthetic (derived from the opium poppy *Papaver somniferum* extract), or fully synthesized.

All opioid agents act on central MOP receptors that, in turn, modulate pain by activating descending inhibition pathways. Many agents, morphine included, act on the other opiate and non-opiate receptors as well. The notorious side effects of opiate use (constipation, nausea, respiratory depression) are thought to also arise from agonizing these same receptors.

The National Cancer Institute (NCI) of the National Institutes of Health (NIH) publishes and frequently updates a comprehensive, peer-reviewed, evidence-based summary of information on pain management. Recommendations regarding pain management in this section are drawn from this important resource [29].

The goal of an opiate regimen is to achieve a steady state of analgesia with the fewest side effects, the greatest ease of administration, and at the lowest cost. Although the European Association of Palliative Care has suggested that there is little difference between full agonist opiates in terms of analgesia or side effects [30], many clinicians develop their own preferences and practices. In choosing among opiates, individual patient effectiveness and side effects, cost, presence of metabolites, underlying health conditions, and ease of administration are all important factors.

Opioid dosing can be highly variable from patient to patient and must be tailored to individual responses and characteristics. A patient who has never taken opiates before will achieve analgesia (and experience side effects) at a much lower dose than someone who has previously been exposed, either through legal prescriptions or illegal means.

A strategy for moderate or severe pain should commence with short-acting opiates given under close observation on an around-the-clock basis with a PRN rescue dose used in the case of breakthrough pain. Once a good balance between analgesia and side effects has been achieved, the total daily dose of short-acting agents can be converted to longer-acting formulations. Short-acting breakthrough opiates are still necessary and should always be available. In general, the short-acting breakthrough dose should be 10–20 % of the total daily dose given as needed every 1–4 h. Starting doses depend on the potency of the agent chosen. A strategy that starts with conservative dosing rapidly escalates to achieve pain control (for moderate pain daily increases by 25–50 % and higher for severe pain), and close monitoring of the patient for side effects, especially respiratory depression and level of consciousness, is recommended. There are no maximum doses for strong opiates.

It is often necessary to switch from one opiate to another or from one route of administration to another. For all opiates other than methadone, relative potencies are well described and calculations based upon them straightforward. The total daily (24 h) dose of the current medication is converted to the equivalent oral morphine amount. That amount is then converted to the equivalent of the new drug based upon the equivalency between it and oral morphine to determine a total 24-h dose of the new drug. This dose is then reduced from 25 to 50 % to ensure safety and then divided by the number of times in a 24-h period the new drug is given.

With rare exceptions, the best route of administration in a patient with a functioning GI tract and the ability to swallow without aspirating is oral. Rectal or transdermal routes are good alternatives; however, transdermal approaches are inadequate for acute or breakthrough symptoms. Opiates [31] should never be administered intramuscularly. If parenteral approaches are needed, IV and subcutaneous routes are equally effective. Because, however, the preparations of opiates used in these routes have greater bioavailability, the doses are one half or less than the oral equivalent. Some patients may benefit from intraspinal or intrathecal administration of opiates. In the largest randomized trial comparing intraspinal to regular pain management, pain was better relieved, there were fewer side effects, and patients lived 102 days longer [32].

Morphine is the best known and globally the most widely used full opioid agonist. It is available in both long- and short-acting formulations and can be administered via a number of routes. Like other full agonists, morphine will not reverse or antagonize other agonists administered simultaneously. It has become the "gold standard" also in the sense that potency of other opioids is measured against oral morphine. Controlled-release preparations typically have initial effect in 1 h, peak in 2–3 h, and last for up to 12 h.

Methadone, another agonist, is an attractive alternative because of its rapid oral and rectal absorption, lack of active metabolites, and low cost and availability in a liquid form. It has not been ruled out as a first-line agent for pain by the NIH expert panel. Difficulties with its use relate to its relatively erratic half-life, difficulty in determining equianalgesic levels with other opioids (the NIH consensus document outlines five different methods of determining initial methadone doses when switching from another opiate to methadone), and possible deleterious cardiac effects related to prolonged QT intervals. It should not be given in the presence of any other drugs that may prolong QT intervals. Consultation with a clinician expert who is experienced in the use of methadone is important, especially if this drug is chosen by an inexperienced provider. While it is commonly thought to have more N-methyl-d-aspartate (NMDA) receptor antagonist activity than morphine, and thus to be more effective in neuropathic pain, the only comparative randomized trial showed no major differences [33].

Short-acting preparations are appropriate for acute pain and for breakthrough or rescue dosing. Their effect usually begins within 30 min of administration and lasts for 4 h.

Fentanyl, because it can be administered transdermally, as a sublingual spray, or as a lozenge, pill, a film that dissolves orally, nasal spray, IM, or IV, can be especially useful in certain situations. A fentanyl patch is, however, not appropriate for acute pain as it takes about 12 h for the effect to start, another 12–24 h for it to peak, and generally lasts for 72 h. Fentanyl is also less absorbed in cachectic patients and required twice as high a dose as normal weight patients in one study [34]. Other full agonists that can be used in cancer pain include hydromorphone, codeine, oxycodone, oxymorphone, hydrocodone, and levorphanol.

Meperidine, which has a neurotoxic metabolite that accumulates over time, is a poor choice, especially with renal failure. Partial and mixed agonist–antagonist drugs like pentazocine, butorphanol tartrate, dezoine, and nalbuphine hydrochloride are also unsuitable because of their inherent maximum ceiling on analgesia effect. Preparations that combine an opioid with a non-opioid agent are limited by toxicities associated with the non-opioid component.

Because opiates retard gut peristalsis, stool in patients becomes dehydrated, and, unless obstruction or diarrhea is present, the patient experiences constipation. All patients taking opiates, therefore, should be given prophylaxis against constipation using, at a minimum, stool softeners. Most will also require mild osmotic agents, polyethelene glycol, and bulk-forming agents or cathartic laxatives such as senna or bisacodyl. It must be remembered that osmotic and bulk agents require oral

hydration to be effective. Sennosides are the mainstay at most hospices because of effectiveness, tolerability, low cost, and there is no added effect of adding docusate to senna [35].

Nausea and vomiting often accompany use of opiates. The mechanisms responsible are stimulation of the chemoreceptor trigger zone – a dopamine-mediated event – reduced gastrointestinal motility, and, rarely, increased vestibular irritation. Metoclopramide, which can be given via oral and parenteral routes, and domperidone, which is only available orally, both improve gastrointestinal motility and have antidopaminergic effects. Consequently, these two drugs are often a first-line choice. In the United States, domperidone is not available except by special dispensation, so it is rarely used. Histamine [36]-blocking agents impact on the vomiting center and vestibular system and have their best utility when vestibular involvement is present. Haloperidol and phenothiazines are also useful, especially when motility-enhancing agents are contraindicated. Anticholinergic side effects often limit the use of chlorpromazine and anticholinergic drugs such as hyoscine hydrobromide.

Neurocognitive side effects of opioid use are not fully understood but appear, in part, to be related to opioid metabolites. Toxicities can include hallucinations, myoclonus, cognition deficits, delirium, allodynia, and hyperalgesia. In the case of a patient who demonstrates the latter symptom after starting or increasing an opiate, toxicity should be considered. Patients with renal failure or advanced disease are especially prone to neurocognitive side effects. Because morphine and hydromorphone have different active metabolites and methadone has none, clinical strategies to switch between these agents have been used to minimize neurocognitive dysfunction. A patient with cancer, especially in an advanced state, who presents with nonfocal neurological symptoms of delirium or other global dysfunction, should be ruled out for side effects of other medications, dehydration, constipation, hypercalcemia, and/or sepsis.

7.4 Adjuvants (Coanalgesics)

These pharmacotherapies are used most often in conjunction with opiates to treat nociceptive pain. In some instances of neuropathic pain, however, select adjuvants can rightly be used as effective first-line therapy [37].

Nonsteroidal anti-inflammatory can serve an adjuvant role in management of cancer pain. A meta-analysis showed that single doses had a rough equivalent to 5–10 mg of intramuscular morphine. The analysis noted, however, a lack of evidence for a role in malignant bone pain. Side effects (GI bleeding, dizziness, and drowsiness) increased with dosage and showed no ceiling effect [38].

Tricyclic antidepressants (TCAs) that retard both norepinephrine and serotonin reuptake act by augmenting modulation of pain impulses at the ganglion. They make an additional contribution to pain management by treating depression itself – a state known to heighten pain perception [39]. TCA's anticholinergic effects often limit their dosage and, hence, impact. The clinical utility of newer antidepressant

agent classes, selective serotonin reuptake inhibitors, and selective serotonin–norepinephrine inhibitors, in pain management, is under investigation.

Gabapentinoids (gabapentin and pregabalin) are antiepileptic drugs that inhibit calcium release at gated calcium channels in pain pathways, depress hyperexcitability, and thus depress neurotransmission. They can be effective agents in management of neuropathic pain, work synergistically with opioids as adjuvants, and are generally well tolerated although somnolence and dizziness can limit dosage [40]. Other anticonvulsants to be considered include carbamazepine, valproate clonazepam, and lamotrigine.

Local anesthetics (mexiletine and lidocaine patch), psychostimulants (dextroamphetamine and methylphenidate), baclofen, calcitonin, clonidine, octreotide, and bisphosphonates have all been used as adjuvants in cancer pain management with varying levels of success. These are reviewed in the NCI Physician Data Query (PDQ) publication.

Corticosteroids have been widely used in managing patients with cancer pain. Aside, however, from a well-established role in managing certain types of disease (e.g., mass effect of CNS tumors and pain ensuing from increased intracranial pressure), the evidence supporting use of corticosteroids as analgesic agents is not strong and more research is needed if a firm role for them is to be adopted [41]. In one well-designed trial, dexamethasone added to metoclopramide was no better than placebo in reducing nausea [42]. Dexamethasone 4 mg bid has the added effect of improving quality of life and reducing fatigue, compared with placebo, near the end of life [43].

7.5 Important and Common Clinical Situations

Tumor invasion of bony structures causes significant pain and morbidity. The clinician should be especially vigilant to identify bone pain and to rule out or address impending pathological fractures (especially if there is spinal disease and a potential for spinal cord compression). In addition to standard pain management approaches as described above, any bony involvement should prompt consideration of bisphosphonates, which are known to prevent skeletal-related events and pain in advanced breast cancer, multiple myeloma, prostate cancer, and lung cancer [44]. These drugs are also beneficial for the hypercalcemia that often accompanies advanced metastatic disease. Calcitonin has also been used to treat pain arising from cancer involving bone. A recent Cochrane review did not, however, find sufficient evidence to endorse this approach [45].

External beam radiotherapy (EBRT) is a well-documented means of addressing pain arising from bone cancer and strengthening bones damaged by tumors. A number of studies have demonstrated that single fraction therapy is equally efficacious and more cost-effective than multiple fraction therapy [46]. Radioactive particle therapy that seeks bone by binding to phosphates can relieve pain and reduce skeletal events [47], and one isotope actually prolonged survival in patients with metastatic prostate cancer [48].

Cancer-related bowel obstruction can result in significant suffering with severe symptoms and pain. In addition to standard analgesic antisecretory drugs, antiemetics and even surgical interventions (venting gastrostomy, stent, diverting ostomies, and more) are often necessary to achieve comfort. Nasogastric tubes are frequently a cause of pain themselves and should only be used on a temporary basis to relieve symptoms [49].

7.6 Looking to the Future

Advances in cancer pain management will come from a better understanding of the pathophysiology of pain, discovery of novel medications and techniques to treat pain, and smarter educational and public policies directed at promulgating pain management techniques into healthcare systems.

There are other novel ways of relieving pain that do not rely on drugs. Spinal cord stimulation, in which an electrode is positioned on the dorsal column of the spinal cord itself, can dramatically reduce pain of all types but must be performed by an experienced group using appropriate safety measures [50]. Similar techniques used for peripheral nerve stimulation have evolved over the past decade often with dramatic success, but there are no randomized comparison trials [51]. A noninvasive type of peripheral nerve stimulation using the body's own C-fibers to conduct electrical impulses labeled as "non-pain" information is similarly promising with apparent dramatic effectiveness in cancer abdominal pain [52], cancer pain [53], chemotherapy-induced neuropathy [54], and other types of neuropathic pain; [55] randomized placebo controlled trials are ongoing.

The new and exciting technologies are not restricted to electrical stimulation. High-intensity "cold" light therapy, or photon stimulation with light-emitting diodes (LEDs), can improve some diabetic pain qualities and improve mood and quality of life compared with placebo light therapy – with just four treatments [56]. Other approaches include augmentation of microglial cells with stem cell transplantation [57], novel sodium–calcium channel blockers at the dorsal root ganglion, nerve growth factor augmentation, and a variety of other novel approaches [58].

Well-designed research ensures the use of *current* technologies by understanding the barriers at the patient, family, provider, payer, and systems levels [59]. Patient involvement and activation methods such as PRO-SELF, a nurse-coaching method, worked well in the United States [60] and Germany [61] but not quite as well in Norway [62]. Having a palliative care team involved alongside the usual oncology care has shown reduced symptoms in most of the randomized clinical trials [63] and is now standard practice [64].

The World Health Organization's executive board adopted a resolution entitled "Strengthening of palliative care as a component of integrated treatment within the continuum of care" on January 23, 2014 [65]. This was a watershed moment for legitimizing palliative care globally and, hence, set the groundwork for improved

cancer pain management around the world. With the imprimatur of the WHO behind it, the effort to build and integrate palliative care into health systems, rather than to isolate it as an "add-on" or optional set of services, gained new strength and visibility.

This advance did not occur in isolation. It was, rather, the culmination of a long and difficult struggle by many individuals and organizations dedicated to improving pain management for people living with serious illness including, but not limited to, cancer. Reaching back to the earliest years of the palliative care movement at St. Christopher's Hospice in London, through the formation of hospice and palliative care institutions and educational programs in Europe, North America and other regions by visionary leaders, to an international coalescence embodied in entities like the United State's National Hospice and Palliative Care Organization (NHPCO), the University of Wisconsin's Pain and Policy Studies Group, the Worldwide Palliative Care Alliance, the American Academy of Hospice and Palliative Medicine, the Diana Princess of Wales Fund, the African Palliative Care Association, Help the Hospices (UK), the President's Emergency Plan for AIDS Relief, and many others, a critical mass of political will and compassion was marshaled and deployed to good effect on the global stage.

This achievement is best viewed as an opportunity for renewed efforts to improve the management of pain with cancer patients by expanding palliative care. In the United States, a survey of academic medical school deans in 2004 found that although 84 % viewed end-of-life care as being "very important," difficulties in providing appropriate education (lack of time in the curriculum, lack of faculty expertise, and absence of a faculty leader) made the issue difficult to address [66].

One of the most important ways that leadership and expertise are fostered is through the creation of focused training programs and specialty certifications. In the United States, board certifications have been established in palliative care for medicine, nursing, social work, and chaplaincy. Since 2012, certification is only available to physicians who have active board membership in an approved field (pediatrics, medicine, etc.) and who have completed an additional year of approved fellowship training in palliative medicine.

This growth in education and professional stature has been paralleled by a significant growth in hospital-based palliative care programs. The Center to Advance Palliative Care has determined that, among US hospitals with 50 or more beds, the number of palliative care programs increased 125 % between 2000 and 2008 [67]. Additionally, the Joint Commission has recently begun a process to recognize hospital inpatient programs that demonstrate exceptional patient- and family-centered palliative care.

These trends are likely to strengthen as the impact of palliative care on healthcare costs is better understood. Rather than being an additional cost center for health systems, recent research points to significant cost savings associated with refocusing goals of care (typically to pain management, comfort measures, etc.) and thus avoiding high cost interventions that do not advance or support them [68, 69].

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Breakthrough Cancer Pain

8

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8.1 The Problem

Breakthrough pain is a relatively new concept, first coined by Portenoy and Hagen in 1990 [1], and anecdotal observation suggests that awareness of breakthrough pain as a distinct clinical entity remains relatively low [2]. Cancer pain is often variable, with a waxing and waning course throughout a day. For example, variations in activity level may be associated with exacerbations of pain that are somewhat predictable. On the other hand, sudden and significant changes in pain intensity may also occur spontaneously. While these are both examples of breakthrough pain, the strategy for addressing each scenario may be quite different. Breakthrough pain may also have variable pathophysiologic underpinnings, sometimes from a neuropathic process, while at other times from more nociceptive or mixed etiologies. Given the complexity and heterogeneity of breakthrough cancer pain (BtCP) as a distinct clinical entity, a separate chapter dedicated to its assessment and management is appropriate. BtCP can have a dramatic impact on the quality of a patient's life, as well as key pain-related outcomes, and therefore warrants focused attention and expert management.

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8.1.1 Definitions

One of the difficulties inherent in approaching BtCP is the absence of a standard definition [3]. Several different definitions appear in the published literature, and these have evolved over time. Payne reviewed the published literature in 2007 [3] and provided a useful synopsis of the different definitions that appear therein. Ultimately, he concludes that BtCP is "most commonly defined as an abrupt, short-lived, and intense pain that 'breaks through' the around-the-clock analgesia that controls persistent pain." Similar definitions have been advanced by national organizations [4] and authors [5] (Table 8.1). Common to these published definitions is the view that breakthrough pain occurs despite appropriate attempts at controlling the more continuous, chronic components of pain. Still, the lack of standard assessment tools and the heterogeneity of existing definitions render this topic somewhat difficult to address [7, 8].

Defining BtCP helps identify its presence, but it is the context of this pain that will drive decisions about the most effective treatments. In general, BtCP falls into a specific category (Table 8.2) and informs treatment aimed to each patient's experience. Thinking about these categories can help clinicians develop the most appropriate and effective approach to a specific patient's pain and situation. We will discuss one such approach in further detail below.

8.2 Evidence

8.2.1 Epidemiology

Given the lack of agreement over the definition of BtCP, its epidemiology is similarly ill defined. Portenoy and Hagen's original description of BtCP cited a 64 % prevalence of breakthrough pain among patients with cancer. A more recent international survey of pain specialists reported a similar prevalence of 64.8 % [9]. The most recent systematic review by Deandrea et al. reports a pooled prevalence estimate of 59.2 %, with a significant amount of variability depending on the site [10]. For example, the pooled prevalence estimate reported by Deandrea and colleagues was noted to be much lower in outpatient clinic settings (39.9 %) and much higher in hospice (80.5 %). Caraceni and coworkers conducted a study of BtCP that required educational sessions with palliative care clinicians to ensure all were using common diagnostic criteria for BtCP; they found a prevalence of 73 % [8]. Other

Table 8.1 Defining breakthrough pain

National Comprehensive Cancer Network	"Episodic pain not controlled with [an] existing pain regimen" [6]
Oxford Textbook of Palliative Medicine	"A transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled background pain as a result of an opioid treatment regimen" [5]

Table 8.2 Breakthrough pain categories [4]

Incident	Pain associated with particular activities, levels of activity, and anticipated or planned events that may be managed preventively via planned doses of short-acting opioids
End-of-dose	Pain that occurs near the end of the long-acting opioid's prescribed dosing interval
Idiopathic	Pain that is intermittent, unpredictable, and not readily managed with preventive strategies

evidence suggests, however, that despite the high prevalence of BtCP, this condition remains under-recognized and thus undertreated [11].

Longitudinal study has shed further light on the experience of patients facing BtCP in daily life [12]. Mercadente and colleagues followed 101 consecutive cancer patients admitted to a home palliative care program in Italy [12]. At baseline, 70.2 % of patients were receiving analgesics and 52 % had uncontrolled pain. Just over 49 % reported a mean number of 2.4 episodes of BtCP per day and an average pain duration of 35 min per episode. Among these, two-thirds had pain with movement; ceasing the movement decreased pain spontaneously in 74 % of the patients with movement-related pain. Over three-quarters (78 %) of these patients noted marked limitation in physical activity due to their pain. Interestingly, most of these patients did not have a prescription for a BtCP medication at time of admission to the home palliative care program. At the time of the second assessment 1 month later, more patients had been started on a BtCP medication, and the incidence of breakthrough pain with movement had decreased significantly. These findings suggest that poor awareness of BtCP as a clinical entity remains a major problem and that BtCP significantly limits the activity level of patients. These results also suggest, however, that medications aimed at addressing BtCP may improve patients' mobility.

BtCP also appears to be particularly prevalent in the hospice setting. One detailed longitudinal study of 22 hospice patients found that 86 % experienced an average number of 2.9 episodes of breakthrough pain per day with an average intensity of 7 on a 10-point scale [13]. The average baseline pain scores for these patients were 3.6 during the day and 2.6 at night, suggesting quite good pain control at baseline, but clearly they also experienced episodes of significant, severe breakthrough pain. Episodes of breakthrough pain lasted 52 min on average, and the average time to relief was upward of 30 min. Interestingly, caregivers' perceptions of the severity, duration, amount of relief, and time to relief were very inaccurate and were generally underestimated.

8.2.2 Characteristics

Despite the lack of a consensus on the definition of BtCP, its descriptions in the published literature include several important features worth highlighting. First, BtCP can have a significant negative impact on a patient's quality of life and can be present at any stage of disease [14]. In one longitudinal study of patients with and

without cancer, investigators assessed the impact of breakthrough pain on ambulatory patient's health-related quality of life [15]. Breakthrough pain was associated with increased somatic complaints in this study. Patients also reported their pain posed significant interference with their function. Other evidence similarly demonstrates that BtCP has negative impacts on patients' mobility [16]. Beyond this, BtCP patients are dissatisfied with both the impact that pain has on their lives and with their pain management in general [17].

BtCP is often described in different categories, either relating to its likely etiology or along more anatomic and pathophysiologic lines. As briefly presented earlier (Table 8.2), Payne describes the three main categories: (1) incident, (2) end-of-dose failure, and (3) idiopathic. The so-called incident pain occurs in relation to a specific activity or event. For example, patients may develop incident pain each time they attempt to change position or get up from a chair. Others may experience incident pain upon turning a certain direction or walking briskly instead of slowly. Still others might experience incident pain with certain stimuli, such as cold temperature or fabric touching an affected area of the skin. Whether the pain is physiologic or neuropathic in origin, it is useful to categorize the resulting pain as "incident." This is because the predictable occurrence of pain in certain settings allows patients to anticipate the pain and to take premedication before doing an expectedly offending activity or to modify their activity to reduce the occurrence of pain.

Idiopathic breakthrough pain, on the other hand, is not predictable. For example, a patient might suffer significant intermittent, cramping abdominal pain. There may not be a clear trigger, though it is important to undertake efforts to identify a less obvious one, which could lead to suggestions about ways to minimize or avoid the pain. In the case of idiopathic BtCP, one cannot readily premedicate or alter routine behavior to improve the pain. Instead, other approaches are necessary, as discussed later below.

End-of-dose failure is a very common and distinct type of breakthrough pain. This occurs when a patient's existing analgesic medication "wears off" toward the end of the dosing interval. For example, a patient may take long-acting morphine sulfate every 12 h but begin experiencing an escalation of pain about 10 h after each dose. In this case, it is not necessarily any particular activity or underlying pathophysiology that is leading to the breakthrough pain, but rather the kinetics of how the opioid behaves in this particular patient. Adjustments to the dosing interval or amount can be highly effective once adequately titrated.

Considering the three aforementioned types of BtCP clearly has important implications for management strategies, given their very different underlying etiologies. Similarly, considering the pathophysiologic etiology of BtCP can also be effective at informing a plan to effectively address it. Pain is often categorized within four main categories: (1) somatic, (2) visceral, (3) neuropathic, or (4) mixed. Somatic and visceral are types of nociceptive pain. Somatic nociceptive pain generally involves injury to structures, such as bones or muscles. Patients classically describe somatic pain as "aching," "throbbing," or "pressure-like" in its quality. Visceral nociceptive pain is due to injury of a viscus. This could involve a more "cramping" pain in the context of hollow viscus obstruction, as in the case of a malignant bowel

obstruction, or perhaps more "gnawing" pain from capsular stretch of the liver or other such organs. Neuropathic pain, on the other hand, is generally due to damage to the nerves themselves. It thus manifests quite differently than nociceptive pain, instead often described like an "electric shock," or "burning," or even as an excessive sensitivity to normal stimuli (often referred to as "allodynia"). So-called mixed pain, as its name implies, is due to multiple etiologies. For example, a patient may experience both somatic and neuropathic pain in the context of a bony tumor that causes nerve infiltration or compression.

While there is no universal agreement on the categories and types of BtCP, it is useful to consider a similar framework when evaluating a patient with unresolved pain. The three general categories (incident, idiopathic, end-of-dose) can help suggest a useful management approach, while the main pathophysiologic categories (somatic, visceral, neuropathic, mixed) can point toward additional key considerations regarding the use of adjunctive analgesics or even interventional procedures that will lead to more optimal palliation of the most bothersome symptoms.

8.3 Assessment

Thorough assessment of breakthrough cancer pain is central to improving quality of life. Careful and complete assessment of these episodes and their triggers can identify possible interventions aimed at ameliorating symptom burden. Though there is no single best method to assess these symptoms, oncologists and pain specialists must use a variety of tools to determine the nature and characteristics of the patient's symptoms. Results of these assessments will help identify the optimal strategies for symptomatic relief and minimize the impact of these symptoms on their patients' lives.

There is no single best tool to elicit and assess breakthrough cancer pain. As stated earlier, there is no uniform and agreed-upon definition of breakthrough cancer pain, and this lack of uniformity has impeded progress in improving related outcomes [18]. Haugen et al. evaluated multiple assessment tools but identified no generally accepted definition or well-validated instrument. Webber and colleagues have recently developed and validated a new instrument for clinical use with patients experiencing BtCP [19]. Their breakthrough pain assessment tool (BAT) is a 14-question assessment that provides a brief, reliable assessment of BtCP that can be used by health-care providers across various clinical settings. To date, the BAT has been evaluated in a single language and country (English, the United Kingdom) and is currently undergoing further validity and reliability assessment across larger populations. Additionally, some patients included in this initial study were unable to complete follow-up assessments given their advanced disease, a common issue for studies conducted in palliative care settings [20]. These limitations impact the potential applicability of the BAT to the diverse population who experience BtCP.

A careful history can identify the type and frequency of breakthrough pain episodes, facilitating a better understanding of what treatments might be best to relieve

this type of pain. It is essential that the history includes information about the timing, quality, location, intensity, and duration of the pain, along with any associated exacerbating or alleviating factors.

8.4 Management

The management of BtCP requires attention to the characteristics, timing, frequency, and intensity of the episodes to identify the best treatment strategy for the individual patient. Careful clinical history and assessment can help guide the clinician to the optimal strategy for each case. Available management strategies include a wide range of approaches, spanning conservative tactics such as lifestyle modification to more intensive approaches including opioid and non-opioid medications.

One of the mainstays of breakthrough cancer pain management is identifying the primary cause of the pain. Similarly, identification of episodic pain triggers can also suggest interventions that reduce the frequency and intensity of episodes. Cancer-directed therapies aimed at treating the underlying malignancy and management of situations that increase episodes of BtCP (e.g., increased physical activity) are of particular importance.

8.4.1 Treatment Strategies

8.4.1.1 Cancer-Directed

Cancer-directed therapies, aimed at improving pain by treating the underlying malignancy, include surgery, radiation, and chemotherapy [21–25]. Key adjunctive therapies include bone-directed modalities like bisphosphonates and RANKL inhibitors for patients with bony metastatic disease [26, 27] or radiopharmaceuticals. Addressing the underlying cause of BtCP is the optimal approach to improving it; thus cancer-directed treatments are the mainstay of BtCP treatment whenever they are feasible.

8.4.1.2 Lifestyle and Non-pharmacological

Lifestyle changes like assistive devices for activities of daily living, treatment of co-occurring and precipitating conditions (e.g., cough and constipation), and integrative medicine modalities (e.g., acupuncture) have been shown to improve BtCP [28]. For example, if pain is precipitated or exacerbated by cough, controlling this symptom may reduce the pain. Similarly, if a particular activity worsens the pain, such as reaching above one's head to obtain objects from a cabinet, an assistive device for easier reach may reduce the amount of pain associated with this activity. These strategies are aimed at decreasing the symptom burden, to promote overall well-being, and generally come at low cost and with minimal risk.

8.4.1.3 Pharmacological

For the pharmacological treatment of BtCP, a number of opioid and non-opioid agents have been used. Non-opioid medications including steroids, nonsteroidal

anti-inflammatory drugs, acetaminophen, and ketamine have been studied to determine their optimal roles in the treatment of cancer pain, including BtCP.

Ketamine A recent randomized, controlled trial of subcutaneous ketamine demonstrated no significant benefit in improving Brief Pain Inventory (BPI) scores when used in combination with opioid analgesics [29]. Additionally, there were approximately twice as many adverse events in the ketamine arm as compared to the opioid-only arm, suggesting that this agent may increase harm without significant improvement in clinical benefit. There is ongoing debate about whether ketamine has a role in the management of cancer pain.

Opioids Opioid analgesics remain the primary pharmacological therapy for moderate to severe cancer pain, including breakthrough cancer pain. With its short half-life and rapid onset of action, there has been great interest in newer agents, such as fentanyl, that are better poised to control phenomena that have sudden onset and short duration such as breakthrough episodes of pain. One of the first trials of transmucosal (TM) agents for the relief of breakthrough cancer pain was conducted by Farrar and colleagues; this study compared oral TM fentanyl to placebo in the relief of breakthrough pain in opioid-tolerant patients on long-acting opioid therapy [30]. A subsequent trial compared oral TM fentanyl to oral morphine dosing using immediate-release morphine preparations, demonstrating both improved pain intensity and improved pain relief in those treated with oral TM fentanyl [31].

Subsequent studies have demonstrated efficacy of buccal fentanyl preparations for relief of BtCP. An open-label titration study of buccal fentanyl in patients experiencing 1–4 episodes of BtCP per day while on opioid therapy demonstrated that 65 % were able to achieve an effective dose. Adverse events were mild and were typical of those usually associated with narcotics including somnolence and constipation [32]. In a recent study of buccal fentanyl in Japanese cancer patients receiving long-acting opioids, over 70 % of participants achieved an effective dose with only mild to moderate adverse effects [33]. These studies demonstrate the efficacy of a buccal preparation of fentanyl for the rapid relief of BtCP.

Additional formulations of fentanyl have been evaluated including intranasal preparations, orally dissolving tablets, and sublingual sprays. Each of these seeks to exploit transmucosal absorption that allows for rapid entry into the circulation by avoiding "first-pass" metabolism through intestinal and hepatic pathways. Kress and colleagues evaluated intranasal fentanyl dosing in a phase III, randomized, placebo-controlled study that demonstrated good tolerability and a statistically significant reduction in pain intensity score at 10 min, compared to placebo [34]. Similarly, an observational prospective cohort study demonstrated that patients treated with intranasal fentanyl spray were successfully treated at low doses; 84.5 % achieved pain relief [35]. Importantly, the impact of pain on daily life was reduced and treatment satisfaction was improved with use of this agent.

An orally dissolving fentanyl tablet has been evaluated in patients with breakthrough pain [36]. This multicenter, open-label study included patients with breakthrough pain due to cancer or other causes. The mean time to demonstration of the

first effect of fentanyl was less than 10 min in 69 % of all patients; 60 % of patients with breakthrough cancer pain experienced drug effects within the 10 min time frame, and the frequency of daily breakthrough pain episodes was also reduced. Adverse events included nausea, vomiting, constipation, and somnolence; only 4.5 % of these patients experienced severe adverse events.

A sublingual fentanyl spray preparation has also been evaluated and shown to be efficacious in the treatment of BtCP. The sublingual preparation has a more rapid onset of action as compared to other formulations, as demonstrated in healthy subjects [37]. In this randomized crossover study, sublingual fentanyl administration yielded a higher plasma concentration at 10 min compared to oral TM fentanyl and also demonstrated greater bioavailability. Plasma concentrations at 60 min were similar, indicating that this agent might have the potential to induce a more rapid response without a long-term drug presence that could lead to adverse events. In a phase III, randomized, placebo-controlled trial of sublingual fentanyl spray, patients had improved objective pain relief and greater perceived treatment effectiveness compared to placebo [38]. The most frequent adverse events reported were nausea (7.1 %), peripheral edema (5.1 %), and increased sweating (5.1 %). Serious adverse events occurred in only 6.1 % of patients treated during the study, none of which were attributed to the treatment.

Rapid-acting opioids are one of the emerging and most promising areas of interest for the control of BtCP; however, careful consideration of each patient's unique pain scenario is needed to inform the optimal, individual treatment strategy. If opioids are deemed necessary, a titration strategy can help to minimize the time to adequate relief. Evidence suggests that total daily opioid doses are not predictably related to the amount needed to improve episodic symptoms [39]. Pooled analysis suggests that the best determinant of opioid dosing for BtCP is the response to previous doses of short-acting therapy. The only factor that did demonstrate some relationship is that the dose needed to relieve pain decreases with increased age. Thus, dosing is individualized to the patient based primarily on previous response to short-acting opioid dosing, rather than being clearly associated with other patient characteristics.

Optimal management of breakthrough cancer pain first requires clinicians to be aware of this entity and to thoroughly assess the nature, etiology, and trajectory of this bothersome symptom. A careful history can elicit factors that inform the ideal non-pharmacological and pharmacological treatment strategies to reduce BtCP and thereby improve patients' physical function and quality of life. When using pharmacological approaches, short-acting agents like fentanyl appear to be better suited to treat breakthrough pain due to their rapid onset and short duration of action, allowing for quick and effective pain treatment with no significant difference in adverse effects compared to traditional opioids [40]. As we have discussed, the published literature suggests a lack of awareness of BtCP as a distinct entity. It is therefore also likely that BtCP is undertreated and also that rapid-acting fentanyl products are underutilized.

If transmucosal immediate release fentanyl products are felt to be inappropriate or are unavailable for a particular patient, one can substitute traditional opioid formulations to address BtCP. However, this is a less ideal way to manage BtCP. Given

the rapidity with which BtCP often occurs, and its sometimes unpredictable nature, the traditional opioid formulations often take too long to reach a therapeutic drug level, thereby providing either inadequate or delayed analgesia when patients really need it.

8.5 Ongoing Research and Future Directions

As we have discussed, there are many ongoing efforts to better understand and validate tools to identify and assess BtCP. Moving forward, we will need more unified agreement on a standard definition of BtCP, to provide a common language and framework around which meaningful clinical trials can be conducted to improve patient outcomes. We must also continue to increase awareness of BtCP as a distinct clinical entity that demands unique and targeted solutions. Furthermore, clinicians need better tools to rapidly assess BtCP so that episodes can be more readily and reliably identified and treated. Evidence points to an undertreatment of BtCP, and it is also quite likely that newer rapid-acting products are underutilized. Efforts to increase awareness of the efficacy and favorable toxicity profile of rapid-onset opioids are needed.

Further study and development of non-pharmacological and adjunctive interventions is also important. While opioids clearly play a central role in addressing BtCP, adverse effects – including somnolence, nausea, vomiting, and constipation – are generally undesirable and sometimes prohibitive. The optimal approach to BtCP is usually multimodal, to minimize the required dose of medications like opioids, thereby minimizing the potential for side effects.

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Delayed Nausea/Emesis

9

Lisa M. Bean and Steve Plaxe

9.1 Introduction

Chemotherapy-induced nausea and vomiting is a source of substantial physical and psychological distress among cancer patients. From a list of chemotherapy-associated effects, patients continue to rank nausea and vomiting as 2 of their top 3 most feared effects of therapy [1]. Without suitable prophylaxis, 70–80 % of all chemotherapy patients will suffer these symptoms [2]. Severe or prolonged effects can interfere with a patient's ability to receive proper treatment, and as many as 20 % of patients have even postponed or refused potentially curative chemotherapy due to fear of further episodes [3].

Aside from compromising adherence to therapy and diminishing physical health, nausea and vomiting contributes to emotional distress and embarrassment, increased anxiety and depression, and a decreased quality of life [4, 5]. The impact on daily living can be substantial. The importance of controlling these symptoms is evidenced by results of a recent study on ovarian cancer, in which patients chose "complete to almost complete control of nausea and vomiting" among their most favorable health states, just below "perfect health" and "clinical remission" [6].

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9.1.1 Types of Chemotherapy-Induced Nausea and Vomiting

Underlying mechanisms of chemotherapy-induced nausea and vomiting appear to differ based on when symptoms occur. One of the most commonly accepted classification systems describes five distinct subtypes:

- *Acute-Onset Nausea and Vomiting.* Acute nausea and vomiting occurs within the first 24 h of therapy. Symptoms begin within a few minutes to hours and are usually worst at 5–6 h following therapy. Patients with acute symptoms are significantly more likely to experience delayed symptoms; therefore, all parameters predicative of acute emesis are also considered risk factors for delayed symptoms [7].
- *Delayed Nausea and Vomiting.* Delayed symptoms begin >24 h to several days after the administration of chemotherapy. They reach maximum intensity in 48–72 h and can last 6–7 days [7]. Delayed symptoms, at least in part, are related to the actions of substance P, whereas acute symptoms are most often associated with serotonin. The exact mechanisms are discussed in subsequent sections.
- *Anticipatory Nausea or Vomiting.* Anticipatory nausea or vomiting occurs *before* a patient's next chemotherapy cycle, as preparations begin for the next treatment. It is most often a learned or classically conditioned response and typically occurs after a prior negative experience. Episodes can be triggered by tastes, odors, sounds, sights of the clinic, or simply thoughts and anxiety related to symptoms [8, 9]. Incidence among chemotherapy patients ranges from 18–57 %, with symptom rate and severity tending to increase in subsequent cycles [4, 8].
- *Breakthrough Nausea or Vomiting*. Nausea and vomiting occurring within 5 days of therapy, despite adequate prophylaxis, is termed breakthrough nausea and vomiting. These symptoms are challenging to reverse, and multiple "rescue" antiemetics are often required [4].
- *Refractory Nausea or Vomiting.* Refractory nausea or vomiting occurs in subsequent cycles after antiemetic prophylaxis and/or rescue treatments have failed in prior cycles, usually after several courses of therapy [10, 11]. Patients with ongoing symptoms require a change in prophylactic antiemetic regimen, as their symptoms are no longer responding to their current therapy.

9.2 Mechanism of Disease

The signaling pathways responsible for nausea and vomiting are activated by noxious stimuli such as inflammation, ischemia, or irritation [7]. The vomiting process involves a pre-ejection phase, a retching phase, and an ejection phase, and the physical act results from rhythmic muscle contractions of the abdominal wall and respiratory system [12]. Nausea is more of a subjective feeling of discomfort. The intricate motor reflex required for vomiting involves a complex network of central and peripheral signaling centers, which include the enterochromaffin cells of the

gastrointestinal (GI) tract, the vagal afferent pathways projecting from the gut to the nucleus tractus solitarii and dorsal motor nucleus of the vagus nerve, and the chemoreceptor trigger zone and vomiting center of the brain [13, 14].

The chemoreceptor trigger zone (CTZ) is located in the area postrema on the dorsal surface of the brainstem, along the floor of the fourth ventricle [13, 14]. Unlike other parts of the blood–brain barrier, this highly vascularized area has fenestrated blood vessels lacking tight gap junctions between cells. This makes the area anatomically specialized to sample elements circulating in the blood or cerebrospinal fluid and allows agents such as opioids and dopaminergic agonists to enter and bind local receptors to induce vomiting [15].

The vomiting center is not a distinct place, but a collection of neurons, thought to be located in the dorsolateral reticular formation near the medullary respiratory centers of the brainstem, that contain receptors for opiates and the neurotransmitters choline, histamine, dopamine, serotonin, and substance P [16]. This is the primary area responsible for integrating the afferent stimuli received from activated receptors via the vagal and spinal sympathetic nerves. It then coordinates the efferent signals sent out to the parts of the body involved in vomiting to produce the emetic response. End organs include the cranial nerves, salivation and respiratory centers, and abdominal muscles [17]. Individual patients require different degrees of stimulation to overcome the response threshold of their vomiting centers, which likely contributes to the range of symptoms observed [7, 13].

9.2.1 Chemotherapy-Induced Nausea and Vomiting

Instigators of chemotherapy-induced nausea and vomiting include gut-derived peptides and breakdown products from cytotoxic chemotherapeutic agents. Neurotransmitters released from the enterochromaffin cells of the gut in response to these emetogenic stimuli bind receptors at the end of afferent sympathetic nerves to initiate the process [17]. Activating signals also emanate from the cerebral cortex and limbic system in response to sensory stimuli (i.e., smell, taste, and physiologic stress or pain), from the chemoreceptor trigger zone and from the vestibular-labyrinthine apparatus of the inner ear in response to body motion. These signals combine with the converging inputs from the GI tract to produce the emetic response.

The three primary neurotransmitters implicated in chemotherapy-induced nausea and vomiting include serotonin (5-hydroxytryptamine), substance P (binds neurokinin-1 [NK-1] receptors), and dopamine [5, 12, 17]. *Serotonin*, which seems to be the main neurotransmitter in *acute* pathways, is released from area postrema cells of the chemoreceptor trigger zone and enterochromaffin cells of the GI tract, to initiate the afferent stimuli that ultimately converge on the vomiting center [4].

Substance P, the most well-known mammalian tachykinin peptide, is found in high concentrations in the vomiting center and vagal afferent neurons of the brain stem and spinal cord. As a neurotransmitter, it is released from the terminal of sensory nerves in response to pain or inflammation and acts as the preferred ligand for NK-1 receptors of the gut, area postrema (or chemoreceptor trigger zone), and nucleus

tractus solitarius [12]. Substance P can induce vomiting by activating neurons that cause vasodilation and rapid contraction of smooth muscles in the gut [18]. When substance P release is mediated by chemotherapy, it does this by binding to various NK receptors, primarily located centrally in the nucleus tractus solitarius, as NK-1 receptors in the gut are thought to play only a small, ancillary role [19]. These activated receptors then transmit signals to the chemoreceptor trigger zone and finally to the vomiting center of the brain, to induce vomiting [19].

The role of *dopamine* is less clear, but inhibition of dopaminergic pathways has been shown to reduce symptoms of nausea and vomiting [4]. Antiemetic agents that act at the dopamine receptor include phenothiazines, benzamides, and butyrophenones. Drugs such as metoclopramide, a benzamide, can affect both dopamine *and* serotonin receptors [17].

9.2.2 Acute and Delayed Pathways

Acute and delayed nausea and vomiting should be regarded as two distinct entities, mediated by different biologic mechanisms or, at the very least, divergent signaling pathways [2, 20]. This is supported by the wide range of symptom severity and duration seen with each, as well as multiple findings of clinical trials involving serotonin and NK-1 antagonists, which suggest distinct underlying mechanisms. Acute and delayed symptoms also respond differently to antiemetic agents, with acute symptoms often more easily controlled than others [20].

The *acute phase* of chemotherapy-induced nausea and vomiting is initiated when cytotoxic substances damage the enterochromaffin cells that line the mucosa of the gastrointestinal tract. This promotes the formation of free radicals and leads to the release of serotonin (5-HT_3), substance P, and cholecystokinin from the damaged cells [20]. Serotonin then binds 5-HT_3 receptors on the terminal side of vagal afferent nerves, which lie in close proximity [21]. The chemical stimuli are then propagated as nerve impulses via afferent sensory pathways to the dorsal vagal complex of the central nervous system, which consists of the vomiting center, the area postrema (or chemoreceptor trigger zone), and the nucleus tractus solitarius.

The sensory inputs are integrated and processed by the vomiting center to either initiate an immediate emetic response, as seen with acute symptoms, or to sensitize the vagus nerve to other transmitters subsequently released [22]. Evidence suggests the latter circumstance is what results in the extended or postponed response seen with delayed nausea and vomiting [22]. It is likely, however, that serotonin signaling pathways play a much larger role in the development of acute symptoms and only a minor role in delayed symptoms.

The *delayed phase* of chemotherapy-induced nausea and vomiting is most often activated by the [substance P → NK-1 receptor] interaction. However, in reality, delayed symptoms are likely multifactorial, with overlapping mediators and signaling pathways that are still not fully understood [2, 5]. Putative mechanisms include disruption of the blood–brain barrier by antineoplastic agents, leading to a mild and reversible cerebral edema and increased intracranial pressure that could

potentiate emetic inputs, as well as disruption of intestinal motility by chemotherapeutic agents, leading to gastroparesis and/or protracted symptoms of nausea and vomiting [9, 23].

Some speculate that delayed symptoms result from the accumulation of emetogenic metabolites from chemotherapeutic agents in the gut. Adrenal hormones may also play a role, as urinary cortisol excretion appears to be inversely related, and noradrenaline excretion directly related, to the intensity of delayed chemotherapy-induced nausea and vomiting [24, 25]. This may be partly due to the anti-inflammatory properties of cortisol, which may promote an antiemetic effect by preventing the release of serotonin in the gut [24]. In contrast, noradrenaline may *cause* an emetogenic effect by increasing the sensitivity of serotonin receptors or promoting serotonin release [25].

9.3 Delayed Nausea and Vomiting

Delayed nausea and vomiting most commonly occurs after the administration of highly or moderately emetogenic chemotherapy such as cisplatin or cyclophosphamide [8, 7], but it can also occur with others (i.e., doxorubicin) given at high doses, or for 2 or more consecutive days [7]. In 1985, the pattern of delayed emesis was described in 86 patients receiving cisplatin therapy [26], and only acute antiemetic prophylaxis on day 1. During the first 24 h, 38 % of patients vomited. Over the next 4 days, 93 % experienced some form of delayed symptom, with 61 % experiencing emesis and 78 % reporting nausea. Symptom intensity peaked at 48–72 h following therapy [26].

This pattern appears to differ based on the type of chemotherapy administered. Cisplatin-related delayed emesis, for example, occurs in a *biphasic* pattern [9]. Studies by Gralla et al. showed patients without antiemetic prophylaxis experienced nausea or vomiting within the first 24 h following cisplatin therapy (120 mg/m^2) [27]. Symptoms began with a short latency of 2–3 h and peaked at 6–8 h after therapy. This acute phase lasts for 10–18 h before subsiding, followed by a distinct delayed phase occurring > 24 h later.

In contrast, symptoms following moderately emetogenic chemotherapy usually occur in a *monophasic* pattern. Described by Martin in 1996, initial symptoms have a longer latency of 6–12 h, and in these cases, nausea and vomiting can persist over 24–36 h without relief [28]. In a study involving 31 breast cancer patients receiving 5-fluorouracil, doxorubicin, and cyclophosphamide, patients were observed for 4 consecutive days without antiemetic prophylaxis, and most had vomiting for ≥ 2 days [28]. A study involving carboplatin showed emesis intensity peaks between 8 and 12 h after chemotherapy. Although symptoms subsided significantly by 24 h, 11 % of patients continued to have emesis for another 48 h. Based on his findings, Martin suggested that two patterns of delayed emesis exist. He recommended reserving the term "delayed emesis" for the biphasic pattern of symptoms following cisplatin therapy and the term "prolonged emesis" for the late or sustained emesis following non-cisplatin therapy [28].

9.3.1 Incidence of Disease

Data regarding the incidence of delayed nausea and vomiting has been sparse. A 2004 study, conducted among patients from 14 oncology practices in six countries, showed 60 % of patients receiving highly emetogenic chemotherapy experience delayed nausea and 50 % delayed emesis. With moderately emetogenic chemotherapy, 52 % experienced delayed nausea and 28 % delayed emesis [29]. A subsequent study in 2007 investigating acute and delayed nausea and vomiting in ten community oncology clinics showed similar results, with 36 % of patients experiencing acute symptoms and 59 % experiencing delayed [30].

A study by the Anti-Nausea Chemotherapy Registry (ANCHOR) found that delayed symptoms occurred more often than acute and that their impact on quality of life was greater (more often from delayed nausea than vomiting) almost twice as many patients experienced *delayed* versus *acute* emesis, with delayed symptoms occurring even in patients who did not suffer acute episodes. Overall, nearly one-half of patients experienced a negative impact on daily life, even with only moderately emetogenic regimens [11].

9.3.2 Risk Factors

Treatment-specific risk factors predictive for acute or delayed nausea and vomiting include (1) the medication dose, (2) the schedule and route of administration, and (3) the specific chemotherapeutic agents used [8]. Patient characteristics associated with increased risk include female gender, age <50 years, history of low or no prior alcohol intake (<1 oz/day), those with poor quality of life, or those with a history of previous chemotherapy-induced emesis [31]. Minor risk factors include any history of poor emesis control, including motion sickness or hyperemesis in pregnancy [8]. At present, there remains a need for a comprehensive risk screening process, as well as a way to assimilate such a process into current cancer care.

A number of predictive factors specific to *delayed* nausea and vomiting have been identified. The most important of which is the presence or absence of acute symptoms in the first 24 h [9]. Approximately twice as many patients who experience acute emesis go on to develop delayed symptoms, compared to those without [32, 33]. In later cycles, the incidence of delayed symptoms is not only dependent on the control of acute symptoms during *that* cycle, but also on the incidence of *delayed* symptoms in *prior* cycles [34]. Other factors predictive of delayed symptoms include higher cisplatin dose, female gender, and younger age [5, 9, 33].

9.3.3 Classification of Emetogenicity

The risk of nausea and vomiting specific to the chemotherapeutic agent is based on its inherent emetogenic potential, the dose intensity and frequency, and its combination with other drugs or radiation therapy [35]. Intravenous medications tend to

cause more nausea than oral medicines [8], and treatment to the brain or GI tract is also more emetogenic, as nerve impulses responsible for nausea and vomiting are concentrated in these locations. Chemotherapy agents are classified into categories according to their potential for nausea and vomiting, in the setting of no prophylaxis. The following classification system, from which national consensus guidelines are developed, is widely accepted as the standard [8]:

1. *Highly Emetogenic Chemotherapy (HEC)*: At least 90 % of patients experience nausea and vomiting when no prophylactic protection is provided.
2. *Moderately Emetogenic Chemotherapy (MEC):* 30–90 % of patients experience nausea and vomiting if adequate prophylaxis not provided. This includes anthracycline- and cyclophosphamide [AC]-containing regimens.
3. *Low Emetogenic Potential:* 10–30 % of patients experience nausea and vomiting without appropriate prophylaxis.
4. *Minimal Emetogenic Potential:* <10 % of patients experience nausea and vomiting without prophylaxis.

9.3.4 Challenges Specific to Delayed Symptoms

Trials have indicated that 60–90 % of patients receiving cisplatin chemotherapy will experience nausea and vomiting if not given adequate prophylaxis [2]. Even with the best antiemetics, however, 40–60 % of patients still go on to develop delayed cisplatin-induced emesis [9]. Although chemotherapy-induced nausea and vomiting is generally well managed in the first 24 h, there is still a lack of optimal management strategies for delayed, anticipatory, or refractory symptoms. Antiemetics are far less efficacious for delayed symptoms, making it even more difficult to provide adequate protection for these patients [36, 37].

This difficulty may stem from the fact that treatment guidelines are based largely on chemotherapy emetogenicity, and currently accepted emetogenicity classification systems are based on *acute* symptoms [11]. Complicating matters further is the multifactorial pathophysiology of delayed nausea and vomiting, which is still not fully understood. Resultant diversity among treatment recommendations has made management a challenge [4, 5].

Studies have also suggested that healthcare professionals severely underestimate the intensity and impact of chemotherapy-induced nausea and vomiting. A study in 2004 concluded that physicians and nurses correctly predicted the incidence of *acute* symptoms, but significantly underestimate the incidence of *delayed* symptoms, regardless of the specific chemotherapy agent used [29]. This likely results from the subjective and frequently unobservable nature of delayed nausea and vomiting, which usually occurs at home and out of view of the provider, making it difficult to appreciate symptom severity or provide adequate relief [29]. Furthermore, the intensity of delayed symptoms may be less severe than that of acute, causing some to underestimate the need for intervention. These factors can lead to delays in diagnosis, undertreatment, and underreporting [30].

9.4 Primary Antiemetic Therapy

Most antiemetics competitively block neurotransmitter receptor sites, thereby inhibiting stimulation of peripheral nerves [7]. Without antiemetics, >90 % of patients receiving highly emetogenic chemotherapy will vomit. With appropriate prophylaxis, this number falls to approximately 30 % [8, 38]. Preventing symptoms is generally more successful than treating them; therefore, scheduled, around-the-clock antiemetic administration is preferred over "as needed" dosing [8]. The most effective regimen should be implemented *prior to* the first course of chemotherapy, as opposed to assessing emetic response after less-than-optimal treatment [8, 39, 40]. This is especially true with anticipatory or conditioned responses. For best results, antiemetics should start 30 min prior to chemotherapy, be continued throughout infusion, and then for the entire time the chemotherapy agents exert emetic activity. The entire period of risk can last *at least* 3 days following the last dose of highly emetogenic chemotherapy and 2 days following the last dose of moderately emetogenic therapy, so prophylaxis should continue for *at least* 2–4 days after completion of therapy [8]. In multiday regimens, delayed symptoms can still occur several days after the final dose, even if symptoms did not appear previously.

Experience has shown that antiemetic efficacy decreases during subsequent cycles, making frequent reassessment critical. Adequate hydration and correction of electrolytes should be maintained [8]. If symptoms are refractory to treatment, despite adequate prophylactic dose and continuous 24 h administration, a trial of combined therapies can be used to block multiple emetic pathways at once. Updated guidelines recommend antiemetics with the highest therapeutic index, and this includes serotonin (5-HT_3) receptor antagonists, corticosteroids, and NK-1 receptor antagonists [8, 39]. These agents are effective, have good safety profiles, and can be administered safely in combination [41]. For those patients with persistent emesis, or inability to swallow pills, possible routes of administration include sublingual, nasal, rectal, intramuscular, intravenous, or transdermal. Suppositories, dissolvable tablets, dermal patches, and nasal sprays can also be of value [8].

9.4.1 Serotonin Receptor Antagonists

First-generation 5-HT_3 receptor antagonists have a well-established role in preventing acute nausea and vomiting, but are far less effective for delayed symptoms [32, 37]. Randomized controlled trials in which 5-HT_3 receptor antagonists were combined with dexamethasone for the prevention of *delayed nausea*, or compared with prochlorperazine in the prevention of *delayed emesis*, failed to show a significant increase in efficacy [37, 42]. Subsequent analyses in 2005 found there was neither clinical evidence nor adequate deliberation of cost-effectiveness to justify the use of first-generation antagonists for > 24 h following chemotherapy [43]. Based on these findings, *first-generation* 5-HT_3 antagonists are *not* recommended as standard prophylaxis for delayed nausea and vomiting.

Introduced in 2003, *palonosetron* is a second-generation 5-HT_3 receptor antagonist which now offers a good alternative for preventing delayed symptoms. Compared with first-generation agents, palonosetron similarly binds 5-HT_3 receptors in the central nervous system and gut, but differs in its significantly prolonged half-life of about 40 h (~10 times longer than earlier agents), and its high binding affinity, which is 30–100-fold greater than first-generation agents [44]. Palonosetron also exhibits positive cooperativity at its binding site, likely triggering 5-HT_3 receptor internalization and causing prolonged inhibition [14, 44]. The resultant high selectivity for 5-HT_3 receptors likely contributes to palonosetron's excellent safety profile and the increased efficacy for delayed symptoms.

Studies comparing palonosetron to ondansetron, dolasetron, and granisetron report superiority of palonosetron for both acute and delayed symptoms, but particularly between 24 and 120 h after chemotherapy, supporting its specific role in delayed prophylaxis. Complete response rates (no emesis, no rescue) with palonosetron were 48–57 % [45, 46]. A randomized non-inferiority trial in 2009 comparing palonosetron and granisetron for acute and chronic chemotherapy-induced nausea and vomiting in 1019 patients showed non-inferiority of palonosetron for acute symptoms and *superiority* of palonosetron for delayed symptoms [47]. These findings led to palonosetron becoming the *preferred* 5-HT_3 receptor antagonist (over first-generation agents) by international guidelines and the US FDA for the prevention of acute symptoms with highly or moderately emetogenic chemotherapy and *delayed* symptoms with moderately emetogenic agents [8, 33, 39]. It is important to note that neither regimen provided effective control of nausea symptoms, with only 31.9 % of patients in the palonosetron group and 25.0 % in the granisetron group experiencing "no nausea" [47].

9.4.2 Neurokinin 1 Receptor Antagonists

Neurokinin 1 (NK-1) receptor antagonists inhibit the action of substance P at its receptor site, both in the vomiting center and in the gut [19, 48]. Although there are several emetic pathways, the [substance P → NK-1 receptor] interaction appears to play a role in the final common pathway regulating vomiting [13]. NK-1 receptor antagonists easily cross the blood–brain barrier and work primarily on centrally located NK-1 receptors [19]. *Aprepitant* was the first commercially available NK-1 receptor antagonist [12]. It is given orally usually with a 5-HT_3 receptor antagonist and dexamethasone on day 1 and with dexamethasone alone for delayed symptoms on days 2–3 [8, 33, 39]. A dose of 125 mg is given day 1, followed by 80 mg on days 2–3.

Multiple phase III clinical trials involving *highly emetogenic* agents have confirmed an approximate 20 % improvement in overall and complete response rates with the addition of aprepitant to a 5-HT_3 receptor antagonist and dexamethasone [49–51], leading international guidelines to consistently recommend aprepitant as part of the prophylactic regimen for initial and repeat courses of highly emetogenic

therapy [8, 39, 40]. In all studies, the comparative benefit was more pronounced in the delayed phase compared to the acute.

A subsequent trial by Warr et al. utilizing *moderately emetogenic* chemotherapy also found that the addition of aprepitant was superior to ondansetron and dexamethasone alone, over the entire 5-day study period (51 % vs. 42 %) [52]. When isolated to the delayed phase, complete response improved with aprepitant (55 % vs. 49 %); however, the difference was not statistically significant. This study helped support the addition of aprepitant for select agents of moderate emetogenic risk, as well.

Aprepitant is metabolized primarily by the CYP3A4 isoenzyme, leading to altered plasma levels when coadministered with other substrates, and dose adjustments may be necessary [53]. Although a number of chemotherapeutic agents are also metabolized through the CYP3A4 system (e.g., taxanes, etoposide, ifosfamide, imatinib, and vinca alkaloids), the theoretical concern that NK-1 antagonists interact with these agents has not been demonstrated [54]. Aprepitant is only for oral use, but a newer NK-1 receptor antagonist, *fosaprepitant*, is an IV alternative, which could be helpful in patients with severe mucositis, impaired swallowing, or GI disturbances. Fosaprepitant is given on day 1 of a 3-day regimen (with a 5-HT_3 receptor antagonist and dexamethasone), followed by oral aprepitant 80 mg on days 2 and 3 [10, 55]. Fosaprepitant also is a moderate inhibitor of CYP3A4, so the same precautions apply.

9.4.3 Corticosteroids

Although not approved by the FDA as antiemetics, corticosteroids represent an integral part of antiemetic prophylaxis, exhibiting considerable efficacy as single agents in both acute and delayed nausea and vomiting [36]. Their mechanism is not fully understood, but it is speculated that agents such as *dexamethasone* and *methylprednisolone* suppress symptoms by limiting inflammation and prostaglandin production and possibly by preventing serotonin release in the gut. They may also modify the blood–brain barrier and inhibit cortical input to the vomiting center, thereby raising the emetic threshold [14, 56] and allowing corticosteroids to exert a "booster-like effect" when coadministered with other antiemetic agents [48].

Serotonin receptor antagonists combined with dexamethasone for acute prophylaxis achieve complete response rates of 80–90 % with moderately emetogenic chemotherapy and 60–70 % with highly emetogenic chemotherapy [57, 58]. Addition of aprepitant further improves control of delayed symptoms, with both highly and moderately emetogenic regimens [33, 49, 51]. Guidelines now unanimously recommend dexamethasone (with a 5-HT_3 receptor antagonist and/or aprepitant) as the preferred agent for acute prophylaxis with agents of high, moderate, and low emetogenicity, as well as for the prevention of delayed symptoms (usually with aprepitant) with highly or moderately emetogenic therapy [8, 33, 39].

Current guidelines support a 20 mg dose of dexamethasone (12 mg when coadministered with aprepitant) for highly emetogenic regimens, and a single 8 mg dose

for moderate regimens [8, 33, 39]. The optimal duration for delayed prophylaxis is not well established, but some recommend 8 mg daily on days 2–4 (with aprepitant on days 2–3) for highly emetogenic regimens and 4 mg twice daily on days 2–3 for moderate regimens [8, 33, 39].

Corticosteroids generally are well tolerated and safe. Trials utilizing dexamethasone prophylaxis for delayed emesis have reported moderate-to-severe insomnia (45 %), indigestion/epigastric discomfort (27 %), agitation (27 %), increased appetite/weight gain (16–19 %), and acne (15 %) [48, 59]. Previous concern that steroids may interfere with the antitumor effects of chemotherapy through immunosuppressive mechanisms has not been confirmed [60].

9.4.4 Dopaminergic Antagonists (Neuroleptics)

Dopamine provides a stimulatory effect in the medullary chemoreceptor trigger zone by binding to multiple local receptors (mostly the D2 subtype) [61]. Dopamine antagonists block these receptors, playing a major role in antiemetic therapy. Examples include phenothiazines, which directly target dopamine, and metoclopramide, a benzamide, which inhibits both the dopamine receptor and the serotonin receptor.

A high level of dopamine blockade results in extrapyramidal effects, disorientation, and sedation, limiting the usefulness of these agents to some degree. Currently, they are used primarily for established nausea and vomiting and not prophylaxis [8]. Cogwheel rigidity, acute dystonia, and tremor respond to anticholinergic medications, and akathisia is best treated by switching to a lower potency neuroleptic, decreasing the dose, or adding a benzodiazepine or beta-blocker such as propranolol [7].

9.4.4.1 Substituted Benzamides: Metoclopramide and Metopimazine

Metoclopramide works as a dopamine antagonist at low doses and a serotonin antagonist at high doses [42]. It has proven efficacy both in the prevention of delayed symptoms and the treatment of breakthrough symptoms [62]. Current Multinational Association of Supportive Care in Cancer (MASCC) and American Society of Clinical Oncology (ASCO) guidelines recommend metoclopramide be reserved for special circumstances, such as known intolerance to other agents, or symptoms refractory to 5-HT_3 receptor antagonists, dexamethasone and aprepitant, given the higher effectiveness of these agents [33, 39]. Serotonin receptor antagonists and metoclopramide are also alternatives to dexamethasone for preventing delayed symptoms with moderately emetogenic therapy. Metoclopramide appears most beneficial in the treatment of breakthrough symptoms occurring during the delayed period in spite of optimal prophylaxis [48, 63]. A relatively high dose (20 mg TID) may be more efficacious for delayed symptoms, but also leads to increased sedation and extrapyramidal effects [42].

9.4.4.2 Phenothiazines: Prochlorperazine and Promethazine

Phenothiazines and *butyrophenones* are not "first-line" agents for chemotherapy-induced nausea and vomiting, but they are still useful for managing breakthrough symptoms occurring during the acute or delayed periods [63]. *Prochlorperazine* is perhaps the most frequently (and empirically) used, and, in low doses, is generally effective in preventing nausea associated with radiation and acute or delayed symptoms induced by agents of very low to moderate emetic potential [7]. High IV doses (0.2–0.6 mg/kg/dose) may be required, especially in those with delayed nausea and vomiting on cisplatin regimens [64]. As with all dopamine-blocking agents, adverse effects are primarily extrapyramidal [7].

9.4.4.3 Atypical Neuroleptics

Olanzapine is an atypical antipsychotic medication of the thienobenzodiazepine class [65]. Although not approved by the FDA to treat nausea and vomiting, receptor-binding studies show olanzapine exhibits strong binding affinity for multiple receptors involved in emetic pathways, resulting in antagonism of dopamine at D1–D4 receptors; serotonin at 5HT2A, 5HT2C, 5HT3, and 5HT6 receptors; acetylcholine at muscarinic receptors; catecholamine at α1-adrenergic receptors; and histamine at H1 receptors [65].

Phase III clinical trials confirm the efficacy and safety of olanzapine, showing its addition to the 5-HT_3 receptor antagonist azasetron plus dexamethasone improved delayed nausea and vomiting in both highly and moderately emetogenic settings. Nausea was also significantly improved with the addition of olanzapine in highly emetogenic (no nausea: 70 % vs. 28 %) and moderately emetogenic regimens (86 % vs. 56 %) [66]. In 2011, a clinical trial randomized patients receiving highly emetogenic chemotherapy to either olanzapine or aprepitant on days 1–4, both combined with palonosetron and dexamethasone on day 1. Although complete response rates (no emesis, no rescue) were similar (acute: 100 % vs. 90 %; delayed: 77 % vs. 73 %), the frequency of patients reporting "no nausea" was significantly improved with olanzapine (60 % vs. 38 %), supporting its specific use for the control of acute and delayed nausea symptoms [67].

Currently, olanzapine is recommended by MASCC and the National Comprehensive Cancer Network (NCCN) for refractory and breakthrough symptoms [8, 33]. A dose of 5 mg daily beginning 2 days prior to chemotherapy, and then 10 mg daily from the start of therapy until 7 days after completion, is commonly prescribed. The most common side effects are typical of antipsychotic medications: fatigue, sedation, dizziness, weight gain, and dry mouth [8, 33, 66].

9.5 Other Agents

9.5.1 Benzodiazepines

Studies have indicated a link between pretreatment anxiety and rates of nausea and vomiting following therapy. Because of this, benzodiazepines are recommended by all three guidelines for refractory, breakthrough, and anticipatory symptoms [8, 39, 40].

Lorazepam is most commonly used, with side effects including sedation and short-term memory loss. A small phase II study showed that *midazolam*, a short-acting benzodiazepine, also resulted in reduced nausea and vomiting in 73 % of patients when added to granisetron plus dexamethasone for refractory symptoms [68].

9.5.2 Cannabinoids

Tetrahydrocannabinol (THC) is the active ingredient in marijuana responsible for its psychoactive properties. Synthetic derivatives such as delta-9-tetrahydrocannabinol (i.e., *dronabinol*) are known as endocannabinoids and they have weak antiemetic activity. In humans, two types of cannabinoid receptors exist (CB1 and CB2) [69]. Endocannabinoids bind CB1 receptors in the central nervous system, specifically the dorsal vagal complex, to produce an antiemetic effect by activating a G-protein-mediated reduction in neurotransmitter release [70]. Despite this, the usefulness of these agents is limited by their significant side effects of sedation, dizziness, hallucinations, and dysphoria [48].

The American Society of Clinical Oncology (ASCO) and NCCN guidelines suggest cannabinoids for patients intolerant or refractory to 5-HT_3 receptor antagonists, corticosteroids, and aprepitant, or for consideration in the treatment of breakthrough symptoms [8, 39]. Available in oral form, *Dronabinol* is usually prescribed at a dose of 5–0 mg/m2 every 3–4 h. Sedation or psychiatric effects occur more often at higher doses.

9.6 Novel and Investigative Agents

Gabapentin is a gamma aminobutyric acid (GABA) analog and anticonvulsant, thought to control voltage-gated calcium channels responsible for the release of excitatory neurotransmitters [4]. When added to ondansetron and dexamethasone in preliminary studies, gabapentin significantly improved chemotherapy-induced emesis [71]. Recently, the North Central Cancer Treatment Group competed enrollment for a phase III randomized controlled trial investigating gabapentin in the prevention of acute and delayed symptoms with highly emetogenic chemotherapy [72].

Carbamazepine is an anti-seizure and mood-stabilizing drug with antiemetic activity thought to result from stabilization of inactivated voltage-gated sodium channels and potentiation of GABA receptors [4]. Case reports describe improved refractory symptoms with carbamazepine, and currently, an ongoing trial in Brazil is evaluating its safety and efficacy in chemotherapy patients [4].

Rolapitant and *netupitant* are NK-1 receptor antagonists with potent binding affinity for NK-1 receptor-binding sites, as demonstrated by positron emission tomography (PET) results following a single dose of netupitant [73]. This powerful selectivity suggests potential long-lasting effects, which could allow improved control of delayed symptoms [10, 73]. Ongoing studies include two randomized clinical trials, one assessing efficacy and safety of a single oral dose of netupitant for

moderately emetogenic chemotherapy [10] and a second evaluating the safety of netupitant (administered with palonosetron and dexamethasone), as compared to aprepitant [4].

9.7 Consensus Treatment Guidelines (Single-Day Chemotherapy)

Data suggests poor compliance with recommendation guidelines in clinical practice, despite studies showing guideline adherence can improve the control of nausea and vomiting by 20 % [74]. Current guidelines were published by the American Society of Clinical Oncology (ASCO) and the Multinational Association of Supportive Care in Cancer (MASCC) with the European Society for Medical Oncology (ESMO) in 2011 and by the National Comprehensive Cancer Network (NCCN) in 2012 [8, 39, 40].

Guideline recommendations are based on the emetogenic potential of chemotherapeutic agents (oral and intravenous), and newer guidelines provide recommendations for the entire period of risk, incorporating dosing schedules for both *acute* and *delayed* symptoms into a single algorithm [33]. As previously discussed, one of the most important prognostic factors for delayed nausea and vomiting is the control of acute symptoms. Therefore, any prophylactic regimen for delayed symptoms must include adequate protection against acute symptoms as well. Due to the involvement of multiple neurophysiologic pathways, combination antiemetic regimens have become the standard of care. Please refer to Table 9.1 for a detailed review.

I. *For highly emetogenic chemotherapy (HEC):*
   (a) A three-drug combination is unanimously recommended at least 30 min prior to chemotherapy to prevent *acute* symptoms:
      (i) 5-HT_3 receptor antagonist (palonosetron)
      (ii) NK-1 receptor antagonist (aprepitant)
      (iii) Corticosteroid (dexamethasone)
   (b) For *delayed* prophylaxis, dexamethasone should be continued on days 2–4, and oral aprepitant should be continued on days 2 and 3.
      (i) If aprepitant is replaced with fosaprepitant on day 1, then only dexamethasone is continued on day 2–4 post-therapy.

II. *For moderately emetogenic chemotherapy (MEC):*
   (a) A two-drug combination of a 5-HT_3 receptor antagonist (palonosetron preferred to first-generation agents) plus dexamethasone is recommended for *acute* prophylaxis.
   (b) For *delayed* prophylaxis, dexamethasone is continued on days 2–3 (ASCO guidelines) or days 2–4 (MASCC, NCCN recommendations).
   (c) NCCN guidelines recommend aprepitant (days 1–3) or IV fosaprepitant (day 1 only) be added to the 5-HT_3 receptor antagonist and dexamethasone for select agents of moderate risk which appear to have increased emetogenicity compared to other agents in their class.

Table 9.1 Antiemetic prophylaxis recommendations

Emetic risk category	Phase	Guideline recommendations		
		MASCC/EMSO	NCCN	ASCO
I. High (>90 %) risk	Acute	5-HT_3RA (palonosetron) + DMZ + APR *(or FOS)*	5-HT_3RA[a] + DMZ (12 mg) + APR (125 mg)	5-HT_3RA (palonosetron) + DMZ + APR
	Delayed	DMZ + APR	DMZ (8 mg, days 2–4) + APR (80 mg, day 2 and 3)	DMZ + APR
II. AC-based regimens[b]	Acute	5-HT_3RA (palonosetron) + DMZ + APR/FOS	5-HT_3RA[a] + DMZ (12 mg) + APR (125 mg)[c]	5-HT_3RA (palonosetron) + DMZ + APR
	Delayed	APR *(none, if Fos used day 1)*	DMZ (8 mg) *or* a 5-HT_3 RA (days 2–4) (*if used day 1, cont APR on days 2–3)*	APR *(days 2 and 3)*
III. Moderate (30–90 %) risk	Acute	5-HT_3RA (palonosetron) + DMZ	5-HT_3RA[a] + DMZ (12 mg)[c]	5-HT_3RA (palonosetron) + DMZ
	Delayed	DMZ	DMZ (8 mg) *or* a 5-HT_3RA (days 2–4)	DMZ
IV. Low (10–30 %) risk	Acute	DMZ *or* 5HT_3RA *or* dopamine antagonist	Metoclopramide, with or without diphenhydramine, DMZ *or* prochlorperazine	DMZ (8 mg)
	Delayed	[d]	[d]	[d]
V. Minimal (<10 %) risk	Acute	[d]	[d]	[d]
	Delayed	[d]	[d]	[d]

Abbreviations: *MASCC* The Multinational Association of Supportive Care in Cancer, *EMSO* European Society for Medical Oncology, *ASCO* American Society of Clinical Oncology, *NCCN* National Comprehensive Cancer Network (lists "with or without Lorazepam" with all prophylactic regimens), 5-HT_3 *RA* serotonin receptor antagonist, *DMZ* dexamethasone, *APR* aprepitant, *Fos* fosaprepitant (IV alternative to aprepitant)

[a]5-HT_3RA – Although palonosetron is preferred to first-generation agents in both MASCC and ASCO guidelines, NCCN guidelines do not specify palonosetron as the recommended 5-HT3 agent (ondansetron, granisetron, dolasetron, and palonosetron listed as acceptable choices)

[b]AC-based regimens, containing anthracyclines and cyclophosphamides, were initially categorized as "moderate risk", but are now routinely treated as highly emetic agents

[c]In the moderate-risk group, NCCN recommends the addition of aprepitant to AC-based regimens and other agents having increased emetic activity compared to others in their group (e.g., carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate)

[d]No prophylaxis recommended

(i) Includes carboplatin, doxorubicin, ifosfamide, and methotrexate, among others.
(ii) Evidence supporting aprepitant in moderately emetogenic settings is still evolving; ASCO and MASCC guidelines leave this to the discretion of the provider.

(d) Aprepitant is unanimously recommended to prevent delayed symptoms with *AC-based* regimens, as most guidelines now consider these agents to be of high emetic risk.

III. *Agents of low or minimal emetogenic risk*
(a) *No* antiemetic prophylaxis is recommended for the prevention of *delayed* symptoms with agents of either low or minimal risk.

IV. *Additional recommendations:*
(a) The superiority of palonosetron over first-generation $5HT_3$ antagonists with both acute and delayed symptoms has been shown in randomized clinical trials, leading to recommendation for palonosetron (with dexamethasone) as the preferred 5-HT_3 receptor antagonist.
(b) If aprepitant *is* added in moderately emetogenic settings, any 5-HT_3 receptor antagonist is appropriate for coadministration (with dexamethasone) on day 1. Aprepitant 80 mg is then continued with dexamethasone alone on days 2 and 3.
(i) Day 1 doses of aprepitant (125 mg) and dexamethasone (8 mg) are decreased on days 2 and 3: aprepitant 80 mg with dexamethasone 4 mg.
(c) The NCCN recommends all regimens (high, moderate, and low emetic risk) be given with or without lorazepam, an H2 blocker, or proton pump inhibitor.

9.8 Non-pharmacologic Approach

A number of alternative therapies are available for patients whose nausea and vomiting is not well controlled. Herbal or natural remedies, such as ginger or peppermint, have been suggested for intractable symptoms of nausea and vomiting [48]. It has been suggested that they possess antiemetic properties stemming from calcium channel blocking activity that results in intestinal smooth muscle relaxation, but data is sparse among chemotherapy patients, and there are currently no studies underway [48].

Behavioral therapy techniques, acupuncture or acupressure, and even massage has shown promise in reducing severity and duration of symptoms [4]. The most frequently studied behavioral interventions include systematic desensitization with progressive muscle relaxation, guided imagery, and hypnosis. These interventions appear to be most effective with anticipatory symptoms [75]. Some studies have shown acupuncture may have a significant effect in reducing acute nausea and vomiting, but it does not appear to have any direct effect on delayed symptoms.

Lifestyle modification, including changes in diet and exercise, can also help alleviate symptoms. The NCCN recommends eating food that is "easy on the stomach" or "full-liquid" foods, eating small frequent meals, and eating food at room temperature [8]. Patients should avoid foods that induce nausea and control the overall amount consumed. A dietary consult may be helpful.

9.9 Symptoms That Occur Despite Prophylaxis

If *breakthrough symptoms* occur after appropriate prophylaxis, drugs from a different drug class should be given as rescue therapy. Patients with delayed breakthrough symptoms (days 2–5) should be considered for a 3-day regimen of a dopamine antagonist such as olanzapine or metoclopramide [10]. A recent phase III trial comparing oral olanzapine (10 mg/day x 3 days) to metoclopramide (10 mg TID x 3 days) found olanzapine to be significantly better at controlling breakthrough symptoms with highly emetogenic therapy [76]. Phenothiazine or dexamethasone may also be effective in this setting [8]. Aprepitant has been approved as an adjunct to $5HT_3$ antagonists and dexamethasone for the *prevention* of chemotherapy-induced nausea and vomiting, but has not been studied for breakthrough symptoms.

If *anticipatory symptoms* occur, behavioral therapy with systematic desensitization or other relaxation techniques and anti-anxiolytics, such as benzodiazepines, are most beneficial. Alternating routes, formulations, or schedules may be necessary if emesis is ongoing. For patients with *refractory symptoms* after prophylaxis failed in earlier cycles, a complete change in antiemetic regimen should be considered [10]. For patients receiving highly emetogenic therapy, olanzapine (days 1–3) can be substituted for the NK-1 antagonist aprepitant [67], and for those with moderately emetogenic regimens, aprepitant, or fosaprepitant, can be added [77]. One could also consider substituting high-dose metoclopramide, or other dopamine antagonists, for palonosetron [39]. Benzodiazepines like lorazepam or alprazolam can be given for anxiety with any cycle.

It is important to remember that antiemetic efficacy may decrease as chemotherapy cycles continue [40]. With refractory symptoms especially, it is also important to rule out nontreatment-related causes of nausea and vomiting. Frequent reassessment of emetic risk, disease status, concurrent illnesses, and medications can help ascertain that the best antiemetic regimen is being utilized [39].

9.10 Multidrug and Multiday Regimens

Multiday, high-dose, and combination chemotherapies pose unique challenges. When several different agents are required for *combination chemotherapy*, antiemetic therapy should be tailored to the chemotherapeutic drug with the highest emetic risk [39]. With *multiday regimens*, patients are at high risk for both acute and delayed symptoms. Recommending a specific antiemetic regimen is difficult in

these patients because acute and delayed symptoms begin to overlap after the first day of therapy. The duration of risk for delayed emesis is also difficult to predict, as it depends on the specific regimen used and the emetogenic potential of the drugs administered.

A combination of a first-generation 5-HT_3 receptor antagonist and dexamethasone +/− aprepitant for acute symptoms is recommended daily for each day of a *multiday* or *high-dose chemotherapy with stem cell transplant* [83]. Dexamethasone alone is standard for delayed symptoms, and this can be continued for 2–3 days following therapy completion [8, 33, 39]. If desired, IV palonosetron may be substituted for the oral 5-HT_3 receptor antagonist before a 3-day regimen, instead of using multiple daily doses. Unfortunately, these options are not very effective for delayed nausea and vomiting. Complete response rates for delayed symptoms with various high-dose regimens are 30–70 %, and most studies report ~50 % [78].

In 2011, palonosetron was given for 1, 2, or 3 days with dexamethasone in 73 patients receiving multiday high-dose chemotherapy before stem cell transplant. Although the study produced only a 20 % complete response rate (no emesis, no rescue), vomiting control was significantly improved, with 40–45 % of patients experiencing "no emesis" during the 7-day study period and having no serious adverse events [79]. In 2012, the subsequent addition of aprepitant to a 5-HT_3 receptor antagonist plus dexamethasone significantly improved complete response rates in patients receiving 5 days of cisplatin therapy [80].

In a study of 78 patients receiving multiday therapy, aprepitant was added to granisetron plus dexamethasone and continued for an additional 2 days following therapy. Complete response rates were 58 and 73 % for highly and moderately emetogenic chemotherapy, respectively [81]. Due to this, aprepitant is suggested for multiday regimens associated with a significant risk of delayed symptoms, with repeated dosing recommended over multiple cycles [39]. If well tolerated, aprepitant (80 mg) can be safely continued on days 4 and 5 following chemotherapy [82].

9.11 Other Considerations

9.11.1 Oral Chemotherapy Agents

An additional challenge in the prevention of delayed nausea and vomiting is the increasing use of oral chemotherapy, both cytotoxic and biologic. Oral agents often are given daily, as part of an extended therapeutic regimen, rather than a single IV dose. This chronic administration obscures the distinction between acute and delayed phases and has caused guideline committees to consider the emetogenic potential of oral chemotherapy separately. Oral agents warranting antiemetic prophylaxis include altretamine, busulfan, cyclophosphamide, etoposide, lomustine, procarbazine, and temozolomide [8].

An oral 5-HT_3 receptor antagonist (i.e., granisetron or ondansetron) is recommended daily for highly or moderately emetogenic oral agents. For low or minimal emetic risk, prophylaxis includes metoclopramide, prochlorperazine, or haloperidol [8].

9.11.2 Challenges of Delayed *Nausea*

Despite marked improvements in the control of emesis with newer antiemetics, the control of acute and delayed *nausea* remains an important, unmet need. In practice, 55–60 % of patients experience delayed nausea following chemotherapy, and only 25–38 % report delayed emesis [29, 83]. A recent study on the effects of delayed nausea and vomiting in cancer patients also showed patients report greater impairment of daily living and quality of life with delayed nausea, compared to vomiting [11]. Delayed nausea is more common than acute; it is often more severe and tends to be more resistant to antiemetic treatment [37].

Among antiemetics, olanzapine has shown excellent efficacy in phase II and III trials in the control of emesis *and* nausea in patients receiving highly or moderately emetogenic chemotherapy [66, 67]. In patients with severe, persistent, or delayed nausea despite standard prophylaxis, consideration should be given to include olanzapine in their antiemetic regimen, as it appears safe and effective for both the prevention and treatment of symptoms [76].

9.12 Summary and Conclusions

Over the past several decades, first generation 5-HT_3 receptor antagonists and dexamethasone have significantly improved the control of acute chemotherapy-induced nausea and vomiting. Unfortunately, these agents alone did not appear to adequately control delayed symptoms. Recent studies, however, have noted improvement in delayed symptoms with the use of three newer agents: palonosetron (a second-generation 5-HT_3 antagonist), aprepitant (an NK-1 receptor antagonist), and olanzapine (an antipsychotic) [10, 66]. The second-generation 5-HT_3 antagonist palonosetron has a longer half-life, higher binding capacity, and a different mechanism of action than first-generation agents and appears to be the most effective agent in its class. Although palonosetron improves complete response rates of both acute and delayed *emesis* in patients receiving moderately or highly emetogenic therapy, data suggest that *all* 5-HT_3 receptor antagonists exhibit poor control of nausea [52, 66, 84]. Clinical trials reporting significantly improved emesis have also reported "no nausea" in only 25 %, 32 %, and 33 % of chemotherapy patients with the use of granisetron, palonosetron, and ondansetron, respectively [47, 52, 85].

The combination of palonosetron, dexamethasone and the NK-1 receptor antagonist aprepitant has shown the most promise in clinical trials for improving acute and delayed emesis in patients receiving single-day chemotherapy over a 120-h period following administration. Many of these same studies have measured nausea as a secondary endpoint and have demonstrated that nausea is not well controlled. Olanzapine appears to be important in controlling nausea and has emerged in recent trials as a safe and effective preventative agent (with a 5-HT_3 receptor antagonist and dexamethasone) for emesis *or* nausea, as well as a very effective agent for the treatment of breakthrough symptoms. Clinical trials using gabapentin, cannabinoids, and ginger have not been definitive regarding efficacy in chemotherapy-induced nausea and vomiting to date. Additional studies are necessary in these

settings, as well as in the control of nausea, with multiday chemotherapy and with bone marrow transplantation.

Complications from chemotherapy-induced nausea and vomiting, particularly in patients who may already be debilitated, malnourished, or have recently undergone surgery or radiation therapy, can necessitate hospitalization and cause a wide range of poor health outcomes [11, 30]. Dehydration and electrolyte imbalance also increase the risk of serious medical complications. Poor control of symptoms in these settings can lead to increased healthcare utilization, patient costs, and level of anxiety [26].

In order to better control acute *and* delayed symptoms, we must first better understand the factors that contribute to susceptibility. We have identified a number of risk factors that may predict symptoms; however, this field needs further development and more comprehensive integration into mainstream cancer treatment. Understanding basic biologic, genetic, and clinical predictors of chemotherapy-induced nausea and vomiting may greatly enhance our ability to individualize treatment and tailor antiemetic prophylaxis to each patient.

Despite substantial progress with new antiemetics, and the establishment of standard clinical guidelines, a significant number of patients still experience symptoms. The ultimate goal of research and treatment should be to control all aspects of nausea and vomiting, so that chemotherapy is better tolerated and patients can receive their entire prescribed course of therapy without modification. For best control, antiemetic regimens should be determined prior to initiating therapy, based on the emetogenic potential of the chemotherapeutic agents and individual risk factors. Among currently available antiemetics, 5-HT_3 receptor antagonists, NK-1 receptor antagonists, and corticosteroids appear most effective, achieving complete protection in a majority of patients.

The management of delayed nausea and vomiting in cancer patients remains a challenge. Patients often experience more symptoms than perceived by practitioners. Many antiemetics are not as effective for delayed symptoms, especially delayed nausea. Treatment guidelines, in which rapidly evolving research is summarized into management recommendations by experts, can be a useful tool for practicing clinicians. At this time, chemotherapy-induced nausea and vomiting can be prevented in approximately 70–80 % of patients with appropriate intervention [49, 51].

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Fatigue

10

Gayle Jameson and Daniel Von Hoff

10.1 Problem

Fatigue, the number one symptom reported by cancer patients, is a subjective experience associated with the underlying disease, anticancer treatments, and other comorbid factors. Cancer-related fatigue (CRF) is defined by the National Comprehensive Cancer Network (NCCN) as "a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual activity" and is the most common cancer-related side effect occurring in up to 80 % of chemotherapy and radiotherapy patients [1]. Over the past two decades, there has been a greater interest in research and an increased awareness of CRF in both professional and lay publications.

CRF is recognized as an underdiagnosed and undertreated problem in most patients living with cancer, not only at the time of diagnosis but throughout treatment and even during disease-free intervals. Unfortunately, many patients continue to suffer greatly from this perplexing symptom. The fatigue experienced by cancer patients is quite distinct from that experienced by those without cancer; patients with CRF describe themselves as "feeling tired, weak, worn out, heavy, slow, or that they have no energy or get-up-and-go" [2]. Cancer patients become tired after much less activity than those without cancer, and their fatigue is longer lasting and not ameliorated by rest or sleep. CRF can significantly interfere with a patient's activities of daily living (ADLs) and may persist for months or years after treatment ends

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[3]. Fatigue is often associated with depression, but the relationship between these two factors remains unclear. It has been observed that preexisting depression may be a risk factor for CRF [4].

CRF negatively impacts quality of life and affects patients on multiple levels. Daily activities that bring joy and satisfaction to life may be compromised and diminished. Fatigue can impact relationships with friends and loved ones and reduce job performance [5]. CRF often causes patients to end employment which can lead to financial problems, loss of health insurance, and decreased access to health care.

The causes of CRF are multiple and complex, and its mechanisms have not been well defined. Disease patterns and treatment effects are clearly related to the onset and intensity of fatigue. However, each patient's experience is different, suggesting a variety of host factors. Various biological and psychological mechanisms contributing to CRF have been identified that are potentially treatable such as anemia, anxiety, drug effects, hypothyroidism, malnutrition, physical deconditioning, etc. (Fig. 10.1). CRF is rarely reported as an isolated symptom but rather in combination with others such as depression, pain, sleep disorders, etc. This cluster effect [6], along with wide variability in the presentation of CRF, adds to the complexity of understanding the biology and host factors of underlying cause.

There is a direct correlation between treatment and fatigue, with different treatment modalities such as surgery, radiotherapy, chemotherapy, immunotherapy, and bone marrow transplantation, exhibiting distinct patterns of fatigue. This fatigue can lead to interruption or intolerance of therapy, thus negatively impacting response to therapy and potentially overall survival. Often, treatment-related fatigue lasts even beyond the cessation of therapy.

Although the incidence of CRF varies between patient subgroups, it affects many throughout the cancer spectrum; it appears worse in minorities, unmarried patients, those with lower household income, and patients with metastatic cancer [4]. The

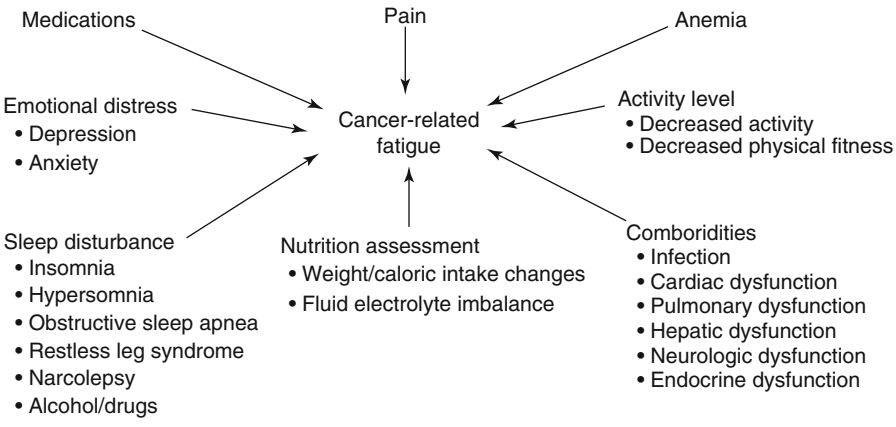

Fig. 10.1 Contributing factors to cancer-related fatigue (Reproduced with permission from Mortimer et al. [1])

incidence of CRF is expected to increase in the coming years with ongoing improvement in cancer treatments and overall survival. Thus, fatigue is recognized as a major problem in cancer patients and survivors.

10.2 Evidence

It must be noted that most studies of CRF have been conducted in populations of breast cancer patients and far less often in patients with other solid and liquid tumors [7].

Fatigue has been reported in patients with most types of cancer and during all stages of disease. In a recent multicenter study, outpatients with breast, prostate, colorectal, or lung cancer undergoing active treatment rated their severity of fatigue and interference with function on a 1–10 scale (1–3 mild, 4–6 moderate, 7–10 severe); 983 of 2177 patients (43 %) reported moderate to severe fatigue. Among those patients with no evidence of disease and not currently receiving cancer treatment, 150 of 515 patients (29 %) had moderate to severe fatigue that was also associated with poor performance status and a history of depression [8].

Cancer treatment-related fatigue appears to display distinct patterns which correlate to the type of treatment the patient undergoes. Patients experiencing fatigue after a successful surgical tumor resection tend to display the most severe fatigue immediately after surgery that subsides over time. Fatigue related to chemotherapy displays a definitive pattern, worst immediately after a cycle of treatment and improving up until the next cycle with fatigue lasting up to a month after treatment [9]. The severity may become worse with each successive treatment cycle, likely due to the accumulation of toxic by-products [2]. Radiation therapy, on the other hand, shows a pattern of fatigue that increases throughout the course of treatment until mid-treatment and then plateaus [10, 11]. It may end after treatment or could extend beyond treatment for months or years. Many personal factors may influence the degree of fatigue. In women receiving treatment for breast cancer, the degree of fatigue is severely correlated with employment during treatment, the presence of children in the home, depression, anxiety, lack of sleep, younger age, and being underweight [12].

Fatigue also persists in patients who are cancer-free and long-term survivors. A longitudinal study of long-term breast carcinoma survivors revealed that 34 % of patients report significant fatigue even 5–10 years post-diagnosis and that the fatigue was worse in patients that had received chemo and radiation combination therapy [13].

10.3 Ongoing Research

Current research efforts in CRF include the study of etiologic mechanisms, development of assessment tools, descriptive studies of patients' experiences, and intervention efforts. A review of ClinicalTrials.gov reveals hundreds of studies related to fatigue and cancer, targeting patients of differing age groups, ethnicities, and

disease types. Some are observational in design, including the study of molecular genetics to identify possible risk factors. Bench research has focused primarily on identifying the mechanisms of CRF. In recent years, chief among these have been studies on the neuroimmune basis of fatigue and the role of inflammation and pro-inflammatory cytokines. Other studies focus on a wide range of interventions such as activity-based and psychological interventions, pharmaceuticals, supplements, acupuncture, light therapy, and diet modification, to name a few.

10.3.1 Neuroimmune Basis of Fatigue

Recent research has expanded our understanding of possible causes of CRF including inflammatory and immune responses from the cancer and/or its treatment. Inflammation is present at all stages of cancer, before treatment, during treatment, and even persisting up to a year posttreatment, which seems to correspond well with the onset and duration of fatigue [4]. In fact, a study comparing the levels of a number of markers in patients' serum found that the pro-inflammatory cytokine IL-6 was the single best indicator differentiating healthy controls, patients with locoregional breast cancer, and those with metastatic breast cancer [14]. This is of particular interest due to the observation that elevation in the blood levels of pro-inflammatory cytokines, secreted proteins which influence the behavior of other cells, are known to generate fatigue-like symptoms in both humans and animal models [15], potentially through alterations in neuronal dopamine synthesis, release, and reuptake [16].

In early-stage cancer the tumor itself appears to be the source of inflammatory cytokines [17, 18], while after treatment cytokines are generated in the course of the response to treatment-induced tissue damage [19]. Clinical observation of patients with untreated breast cancer, acute myeloid leukemia (AML), and myelodysplastic syndrome reveals that inflammatory markers such as C-reactive protein (CRP) and a number of interleukins are present pretreatment [20–22].

It is well known that many cancer patients who undergo radiation or chemotherapy exhibit a marked increase in their fatigue [12] and a sharp increase in circulating levels of inflammatory markers [23, 24]. The levels of these markers of inflammation appear to correlate with severity of CRF from patient to patient [25]. In a within-subject study of early-stage breast cancer and prostate cancer patients before, during, and after radiation therapy, elevations in the levels of inflammatory markers CRP and IL-1RA correlated with increases in fatigue; however, elevations in IL-6 and IL-1β did not [26], indicating that there may be no single pathway by which inflammation contributes to fatigue.

Studies in animal models have been somewhat informative in unraveling the effects of inflammation and appear to confirm a role for inflammatory cytokines in CRF. Growth of ovarian tumors in mice causes increases in the levels of a number of inflammatory markers, including IL-6 and TNF-α, both locally and in systemic circulation and that these animals, while still physically capable of movement,

display a reduction in spontaneous locomotion [27]. Total body irradiation of mice, the best model of radiation therapy, causes an increase in several inflammatory markers, including plasma IL-6, that lasts up to 24 h after treatment [28]. Increase in those markers correlates with a reduction in locomotion, the most common metric of animal fatigue, that persists up to 2 weeks after treatment mirroring the human tissue recovery response to irradiation [28, 29].

Overall, while the correlation between CRF and inflammation in patients remains strong, whether inflammation causes that fatigue remains unclear, and in fact one study of newly diagnosed breast cancer patients found no correlation between levels of CRP and fatigue severity [30]. This confusion exists in no small part due to uncertainty of the neurological mechanism by which inflammation causes fatigue. Further work, both at the clinical and preclinical level, is needed to uncover the mechanisms by which cancer and its treatments influence inflammation both locally and systemically, determine how inflammation affects CRF, and identify biomarkers for diagnosis and targets for intervention that may reduce fatigue.

10.3.2 Activity-Based and Psychological Interventions for CRF

10.3.2.1 Exercise

To date, the most convincing data of an effective intervention for CRF is that related to exercise. Exercise has been shown in multiple studies to improve patients' level of fatigue [31–33]. In 2009 the American College of Sports Medicine (ACSM) convened a round table and, after an in-depth review of the literature, concluded that exercise training during and after adjuvant chemotherapy is safe and results in improvement in physical functioning, quality of life, and cancer-related fatigue in several groups of cancer survivors. ACMS recommended that cancer survivors avoid inactivity and follow the 2008 Physical Activity Guidelines for Americans with exercise adaptations based on disease and treatment-related adverse events [34]. These recommendations include aerobic exercise at least 150 min per week and strength training at least two days per week.

Exercise has been studied in a variety of patient populations and at various time points throughout the cancer experience. One prospective study explored whether the type of cancer affects exercise-mediated improvements in cardiorespiratory function and fatigue; 319 cancer survivors with 7 different types of cancer participated in fatigue inventories, cardiorespiratory function assessments, and an individualized, multimodal exercise intervention with cardiorespiratory, flexibility, balance, and muscular strength training 3 days per week for 3 months. Cancer types included breast cancer (BC, $n=170$), prostate cancer and other male urogenital neoplasia (PC, $n=38$), hematological malignancies (HM, $n=34$), colorectal cancer (CC, $n=25$), gynecological cancers (GC, $n=20$), glandular and epithelial neoplasms (GEN, $n=20$), and lung cancer (LC, $n=12$). Trends toward improved cardiorespiratory function and fatigue reached statistical significance in some groups, and no significant differences were seen between cancer types, suggesting that these

improvements are not dependent on specific cancer types. Mean fatigue indices decreased by at least 17% in all groups, with changes significant in BC, HM, CC, and GC groups. The authors concluded that it is appropriate to prescribe exercise interventions to cancer patients based on individual needs without emphasis on cancer type and recommend further research to investigate a relationship between cancer type and exercise-mediated rehabilitation [35].

One meta-analysis reviewed the effectiveness of exercise intervention on overall health-related quality of life (HRQOL) in cancer survivors who had completed primary treatment. The review included 40 trials with 3,694 participants exposed to exercise interventions. At 12 weeks, cancer survivors who participated in an exercise intervention had greater improvement in overall HRQOL including a significant reduction in fatigue [36].

10.3.2.2 Yoga

Many studies suggest that yoga practice offers multiple health benefits. A large randomized controlled trial in breast cancer patients studied yoga's impact on inflammation, mood, and fatigue [37]. Two hundred breast cancer survivors who had completed cancer treatment (between 2 months and 3 years from last therapy), including surgery, adjuvant chemotherapy, or radiation therapy, were assigned to either 12 weeks of 90 min twice per week hatha yoga classes or a wait list control with no yoga intervention. The study included the biological measures interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and interleukin-1b (IL-1b). Findings showed that immediately posttreatment, fatigue was not lower but vitality was higher in the yoga group. At 3 months posttreatment, comparing the women who had practiced yoga to the non-yoga group, fatigue was 57% lower, and pro-inflammatory cytokines were decreased up to 20% in the yoga group. A secondary analysis noted that more frequent yoga practice correlated with larger changes [37].

10.3.2.3 Qigong/Tai Chi

A double-blind, randomized control trial (RCT) tested 12 weeks of Qigong/Tai Chi (QC/TCE) versus sham Qigong (SQG) on fatigue, depression, and sleep among 87 postmenopausal, breast cancer survivors with persistent fatigue. Participants' mean characteristics included: age 58, BMI 26.8, time to last treatment 2 years, and baseline fatigue 4.2, as measured by the Fatigue Symptom Inventory (FSI) on a 1–10 scale with ≥3 being clinically meaningful. QC/TCE showed a significant improvement in fatigue levels over time (baseline 4.6, at 1 month 2.1, at 3 months 2.3), compared to SQG (fatigue levels of 3.8, 2.6, 2.5, respectively). Both interventions showed improvement in depression and sleep quality. The authors conclude that adding gentle, low-intensity exercise in this patient population, as was done in both groups, may be beneficial in reducing several symptoms. However, the QC/TCE intervention, adding the focus on breath and meditative states to create a deep sense of relaxation, showed an advantage over gentle physical activity in improving fatigue levels in these breast cancer survivors [38].

10.3.2.4 Acupuncture/Acupressure

Acupuncture and acupressure have been studied in CRF with results suggestive of benefit in treating cancer-related fatigue. In a recent review of 11 RCTs conducted in adults with CRF, eight studies utilized acupuncture and three acupressure; the authors concluded that due to the methodological flaws of these studies, no firm conclusions could be drawn regarding the effectiveness or the optimal intensity and duration of the intervention. However, acupuncture and acupressure were noted to be safe in this patient population and warrant further investigation [39].

10.3.2.5 Psychosocial Interventions

Psychological issues arising from the cancer and its treatment contribute strongly to cancer fatigue. Fifteen to twenty-two percent of cancer patients become depressed and the stress, anxiety, and fear that follow a cancer diagnosis contribute as well. The cortisol response to stress is known to be blunted in cancer patients, further exacerbating cancer fatigue [40, 41].

Psychosocial interventions, including education on self-care, coping techniques, and energy management, have demonstrated beneficial effects on fatigue. For example, an Internet-based educational program providing information regarding fatigue, energy conservation, physical activity, nutrition, sleep hygiene, pain control, and stress management versus no intervention demonstrated a reduction in fatigue in the intervention group [42].

10.3.3 Pharmacologic Agents

A number of pharmacologic agents including psychostimulants, corticosteroids, supplements, and antidepressants have been tested in the treatment of CRF with mixed results.

10.3.3.1 Psychostimulants

Over the past two decades, there has been a growing interest in the use of psychostimulants in treating CRF. Methylphenidate, a dopamine and norepinephrine reuptake inhibitor, has been the most studied pharmacologic agent in the treatment of CRF. Although several studies demonstrated benefit [43], most recent large RCTs have been disappointing, showing no statistically significant benefit of psychostimulants in the treatment of CRF [44–46]. One study that showed no overall benefit of methylphenidate in patients with CRF did note a positive effect in a subset analysis of patients with more severe fatigue in advanced cancer [46].

Although recommended by the National Comprehensive Cancer Network in 2014, current data does not support the general use of psychostimulants in treating fatigue outside a clinical trial unless new data supporting use become available [47]. However, in certain situations such as severe fatigue in advanced disease, a psychostimulant may briefly palliate the patient's fatigue and improve quality of life.

10.3.3.2 Corticosteroids

Although limited evidence is available, corticosteroids are often used to palliate cancer-related symptoms [48]. Two recent placebo-controlled double-blind randomized trials in advanced cancer patients demonstrated benefit of corticosteroids in alleviating cancer-related symptoms, including fatigue in advanced cancer patients [49, 50]. Hydrocortisone, cortisone, prednisone, methylprednisolone, and dexamethasone have been studied with no evidence of a difference between these agents in the management of fatigue. Dexamethasone has been studied most extensively. The mechanism of action of corticosteroids in improving cancer-related fatigue is unclear. Several mechanisms have been suggested including modulation of pro-inflammatory cytokines including IL-6, TNF-a, and C-reactive protein [51], decrease in tumor mass and associated edema, and modulation of adrenergic activity in the dorsal horn [48].

A study of patients with advanced cancer experiencing fatigue compared dexamethasone 8 mg daily x 14 days versus placebo. Significant improvement in CRF was noted at both days 8 and 15 in the dexamethasone-treated patients [50].

Another study compared the effects of oral methylprednisolone 32 mg daily versus placebo on analgesic efficacy, fatigue, and anorexia, for a period of seven days in 50 patients with advanced cancer. Significant improvement in CRF and anorexia as measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 was noted: fatigue (−17 vs. 3; $P=0.003$) and anorexia (−24 vs. 2; $P=0.003$). No significant improvement was observed in pain intensity, and no significant difference in adverse events between the two arms was seen [49].

These studies have looked at the benefit and safety of only very short-term use of corticosteroids. The long-term use and associated risks of corticosteroids in palliating CRF have not been studied. However, these risks in the general population are known to include hyperglycemia, prolonged HPA axis suppression, myopathy, infections, osteoporosis, aseptic necrosis, and mood changes. Future studies are needed to evaluate the benefits and risks of moderate- and long-term use in patients with CRF [48].

10.3.4 Supplements

Although there is significant interest in the utilization of herbal and dietary supplements in treating fatigue, few controlled studies have been conducted in cancer patients.

10.3.4.1 Ginseng

A large RCT of 364 cancer patients from 40 institutions evaluated the effect of Wisconsin ginseng 2,000 mg/day on fatigue in cancer survivors. Statistically significant improvement in fatigue was seen at 8 weeks in the ginseng group compared with placebo. Greater benefit was noted in the patients receiving active treatment compared to those who had completed treatment. No discernable toxicities from the ginseng were observed [52].

10.3.4.2 L-Carnitine

In an RCT of cancer patients with moderate to severe fatigue ($n=376$), most with metastatic disease undergoing chemotherapy or radiotherapy, patients received L-carnitine (2 g/day) or placebo for 4 weeks. The intervention group demonstrated no improvement in fatigue compared to placebo [53].

10.3.5 Antidepressants

Antidepressants as treatment for CRF are being studied in animal models, but limited data are available in human trials. One placebo-controlled RCT of paroxetine 20 mg daily in patients with mixed solid tumors showed no difference in CRF between the placebo and paroxetine groups [54].

10.3.6 Sleep

Lack of quality sleep can impact one's level of fatigue. Cancer treatment and CRF both correlate strongly with a range of sleep disorders often brought on by a disruption in circadian rhythms. Commonly reported issues are insomnia, hypersomnia, and disrupted sleep patterns [55]. Sleep disorders including insomnia are more common in cancer patients compared to the general public [56]. This may be due to the psychological, behavioral, and physical effects of a cancer diagnosis and treatment. The American Association of Sleep Medicine recommends cognitive behavioral therapy for insomnia (CBT-I). CBT-I is defined as "a non-pharmacological treatment that incorporates cognitive and behavior-change techniques and targets dysfunctional attitudes, beliefs, and habits involving sleep" [56].

Results of a systematic review of CBT-I in cancer patients suggest that CBT-I is associated with statistically and clinically significant improvements in subjective sleep outcomes and may improve mood, fatigue, and overall QOL in patient with cancer [56].

10.3.7 Cancer Cachexia/Nutrition

Cancer cachexia (CC) is a multifactorial paraneoplastic syndrome characterized by anorexia, body weight loss, and loss of adipose tissue and skeletal muscle and is associated with impaired function, quality of life, and fatigue [57]. Interventions under study in cancer cachexia include anabolic steroids, appetite stimulants, ghrelin analogs, and anti-myostatin agents, to name a few. Anabolic steroids are being studied in cancer cachexia but end points are muscle mass and strength and weight and have not included fatigue measures. Novel agents inhibiting myostatin which is a normal negative regulator of muscle growth have shown the ability to increase muscle volume [58]; however correlation between change in the volume of muscle mass and level of fatigue is yet unknown.

Physical activity is reduced in many cancer patients at some time throughout their disease experience. There are few studies that discern the potential contribution of muscle disuse and muscle wasting to CRF. Research is needed to better define skeletal muscle changes that may contribute to CRF and the utility of exercise and other muscle-building strategies in treating fatigue associated with muscle disuse and wasting [59].

10.4 Solutions

Although the full mystery of CRF is yet to be unraveled, much has been learned regarding contributing factors, biochemical mediators, and actions that patients and health-care providers can implement to improve frequency of diagnosis, identification of treatable causes, and implementation of evidence-based interventions in managing CRF.

10.4.1 Assessment

Current recommendations include that all patients at the time of diagnosis of cancer undergo an evaluation of the level of fatigue and continue regular assessments throughout treatment and recovery [1, 60]. A variety of validated assessment tools are available to health-care providers to assess for the presence and severity of fatigue, from a simple 1–10 rating scale which is the gold standard to more complex multidimensional scales commonly used in research (Table 10.1). Patients who report moderate or severe fatigue (e.g., ≥4 on a 1–10 scale) should be further assessed and examined for any underlying conditions and treated appropriately.

10.4.2 Evaluation and Treatment of the Cancer Patient with Fatigue

Evaluating a cancer patient with existing fatigue requires a careful history and physical examination looking for symptoms and signs that suggest contributing factors

Table 10.1 Examples of validated instruments to assess fatigue [65–73]

Fatigue instruments
Brief Fatigue Inventory [65]
The Functional Assessment of Cancer Therapy – Fatigue [66]
The Piper Fatigue Scale (long and short versions) [67, 68]
The Schwartz Cancer Fatigue Scale [69]
Fatigue Symptom Inventory [70]
Lee's Visual Analogue Scale for Fatigue [71]
Cancer Fatigue Scale [72]
Multidimensional Fatigue Symptom Inventory – short form [73]

to the fatigue (Table 10.2). Patients are most worried about the status of their cancer and fear that recurrence or progression of disease is causative. Concurrent medications, especially narcotics, can contribute to sedation and fatigue. In some cases, adding a nonnarcotic such as an NSAID, if not contraindicated to the patient's analgesic regimen, can decrease the need to escalate the dose of narcotic. A review of the patient's alcohol and illicit drug use along with any social or financial stresses and symptoms of depression can open a discussion of available resources of support in the community. Sleep quality and disruption should be assessed. Patients who are dehydrated note significant fatigue and can benefit promptly with IV hydration. Attention to the patient's endocrine function can reveal an undiagnosed hypothyroidism or a low testosterone level. Of note, men who are chronically ill or on chronic narcotics commonly have low testosterone levels that can easily be supplemented. Hemoglobin and hematocrit levels should be assessed and anemia treated according to the ASCO/ASH guidelines [61]. Identifying and treating other organ

Table 10.2 Assessment/evaluation checklist for patients with CRF

Evaluation checklist	
Assessment of cancer disease status	☐
Patient self-assessment 1–10 analogue scale	☐
Concurrent medication review with special attention to: Analgesics/narcotics	☐
Sedatives/sleep aids	☐
Antihistamines	☐
Psychosocial history Depression/anxiety	☐
Social/financial issues	☐
Alcohol intake	☐
Illicit drug use	☐
Review of systems/Physical exam Fatigue – detailed description of onset, duration, aggravating/relieving factors, impact on QOL	☐
Anemia	☐
Pain	☐
Sleep quality and quantity	☐
Fluid/electrolyte disturbance	☐
Endocrine dysfunction – thyroid, adrenal axis, gonadal	☐
Other organ dysfunction – cardiac, hepatic, neurological, renal, pulmonary	☐
Laboratory Hemoglobin/hematocrit	☐
Sodium/potassium/magnesium	☐
Thyroid function tests	☐
Testosterone level	☐
Cortisol level/cortrosyn stimulation test	☐

Table 10.3 Management of CRF

Management checklist	
Treat co-morbid conditions when possible	☐
Prescribe exercise: Aerobic, 30 min/day, 5 days/weeks	☐
Mind/body interventions: Meditation, yoga, qigong/tai chi	☐
Nutrition consult	☐
Maximize sleep	☐
Educate on self-help techniques	☐
Psychosocial counseling such as cognitive therapy	☐
Consider psycho-stimulant if narcotic-related or advanced disease	☐

system dysfunctions, such as CHF from prior anthracycline use, can make a significant impact in the patient's level of fatigue. A thorough assessment and identification of contributing factors of fatigue in each patient will lead to potential individualized management strategies (Table 10.3).

10.4.3 Strategies to Help Patients Cope with Fatigue

Along with treating and managing the medical causes of fatigue, many patients find that lifestyle changes can help them better cope with fatigue.TherapyandCounseling Talking with a therapist or counselor specially trained to work with cancer survivors can help reduce fatigue. Specifically, a type of counseling called cognitive behavioral therapy or behavioral therapy can help patients reframe their thoughts about fatigue and improve poor coping skills and/or sleep problems that could contribute to fatigue.

10.4.3.1 Mind-Body Interventions

In addition to the already discussed mindfulness-based approaches such as yoga, meditation, etc., massage, music therapy, relaxation techniques, and a form of touch therapy called reiki are harmless and may also benefit patients experiencing fatigue, but more research is needed on these strategies.

10.4.3.2 Patient Education

Educating patients and family members to regularly discuss the presence and degree of fatigue with their health-care providers is key to accurate reporting and symptom management. Patients can empower themselves with knowledge of evidence-based treatments and self-help strategies (Table 10.4). Patients must be instructed that supportive care and symptom management are an important part of overall treatment and quality of life throughout the cancer experience and beyond. Multiple reliable resources addressing CRF are available to patients and family members (Table 10.5).

Table 10.4 List of simple recommendations to help cancer patients minimize fatigue

Recommendations for patients
Avoid inactivity
Gradually increase your activity. Do so gradually in order to conserve energy
Keep a log of which time of day seems to be your best time Plan, schedule and prioritize activities at optimal times of the day
Eliminate or postpone activities that are not your priority
Change your position and do not just stay in bed
Use sunlight or a light source to cue the body to feel energized
Try activities that restore your energy, such as music, or spending time outdoors in nature or meditation
Allow caregivers to assist you with daily activities such as eating, moving or bathing if necessary.
Plan activities ahead of time
Encourage your family to be accepting of your new energy pace
Rest and sleep better
Listen to your body – rest as needed
Establish and continue a regular bedtime and awakening
Avoid interrupted sleep time and try to get continuous hours of sleep
Plan rest times or naps during the day late morning and mid afternoon
Avoid sleeping later in the afternoon which could interrupt you night time sleep
Ask if using oxygen when you sleep will help you to sleep better
Try nutritious, high protein food
Small frequent meals
Add protein supplements to foods or drinks Ask about possible use of medications to stimulate your appetite or relieve fatigue

Adapted from www.HPNA.org[74]

Table 10.5 Patient resources

Patient resources for more information
American Cancer Society (ACS) http://www.cancer.org
American Society of Clinical Oncologists (ASCO) http://www.cancer.net
Cancer Care http://www.cancercare.org
National Comprehensive Cancer Network (NCCN) http://www.nccn.org/patients
National Cancer Institute (NCI) http://www.cancer/gov

10.4.4 Supporting Exercise Behavior Change

Based on the current evidence, cancer care professionals can expect that fewer than 10 % of cancer survivors will be active during their primary treatments, and only about 20–30 % will be active after they recover from treatments. Consequently,

Table 10.6 American cancer society guidelines on nutrition and physical activity for cancer survivors (Reproduced with permission from [62])

Achieve and maintain a healthy weight.
If overweight or obese, limit consumption of high-calorie foods and beverages and increase physical activity to promote weight loss.
Engage in regular physical activity
Avoid inactivity and return to normal daily activities as soon as possible following diagnosis.
Aim to exercise at least 150 min per week.
Include strength training exercises at least 2 days per week.
Achieve a dietary pattern that is high in vegetables, fruits, and whole grains.
Follow the American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention.

unless behavioral support interventions are provided, the majority of cancer survivors will not benefit fully from regular physical activity. Patients may be fearful of injury or harm while exercising, especially if their lifestyle has been sedentary. Some successful strategies include short-term supervised exercise (e.g., 12 weeks), support groups, telephone counseling, motivational interviewing, and cancer survivor-specific print materials [62]. Health-care providers can be instrumental in motivating and guiding patients in developing a safe, sustainable exercise program. Assessing current exercise habits and building slowly toward the goal of 30 min of aerobic exercise five days a week are feasible with many patients during and after cancer therapies (Table 10.6). Recommending 5–10 min of walking two to three times a day may be more appealing to the patient. Utilizing the expertise of an exercise physiologist or personal trainer aware of the individual needs of the patient can enhance patient motivation and cooperation with treatment goals. Another strong motivator for exercise in this patient population is the evolving evidence that exercise offers a potential survival benefit as demonstrated in an exercise study of breast cancer patients likely due to exercise's effect on reduction of inflammation and modulation of the insulin pathway [63].

10.5 Future Directions

Increased research in recent years has provided a greater understanding of the characteristics, prevalence, and course of fatigue in cancer patients. Ongoing work is beginning to uncover underlying mechanisms, risk factors, and effective treatments [4]. A more complete understanding of the mechanisms of CRF will lead to the identification of many more targets for therapeutic intervention.

Still many questions remain unanswered regarding the specific causes and patient predisposition to developing CRF. Further research is desperately needed in the following areas:

- Genomic and epigenomic factors that may predispose an individual to CRF and influence response to therapeutic interventions. It will be very useful to be able

to identify those subgroups of patients at higher risk and those more likely to benefit from specific interventions.
- The role of inflammation and pro-inflammatory cytokines. Greater understanding of which cytokines are causative in specific patients, diagnoses, and treatments.
- Pharmacologic and non-pharmacologic interventions.
- Prevention strategies.

Knowing that the variables affecting CRF are numerous, well-designed smaller studies of more homogenous groups of patients may reveal more accurate and applicable data. Also, a greater consensus in the selection of assessment tools will allow for more consistent results and clearer data analysis between studies. The FDA encourages investigators to use standardized, validated patient-reported outcome measures in symptom intervention clinical trials [64].

Although advances have been made in the identification and treatment of CRF, many cancer patients continue to suffer with fatigue. Ongoing research is surely needed in order to fully understand, prevent, and treat this multidimensional phenomenon lacking an integrative approach.

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Changes in Cognitive Function Related to Chemotherapy

11

Lisa M. Hess and Steven Chin

11.1 The Problem

Chemotherapy-related cognitive impairment, or CRCI, is not yet well understood. It is a phenomenon that occurs among a subset of cancer patients who have received chemotherapy. In general, it is defined as a clinically meaningful or statistically significant decline in cognitive function – such as memory, attention, verbal memory, executive function, or information processing speed – that is associated with chemotherapy treatment [1–3]. However, cognitive function is complex and is affected by a number of other changes patients experience, such as hormonal changes, stress/distress, worry, anxiety, depression, fatigue, aging, and the effects of anesthesia during surgery, all of which are known to affect cognitive function [4–7].

One of the earliest known reports of this issue was published by Dr. Silberfarb who examined the cognitive impact of cancer therapy in the early 1980s [8]. Over time, publications have been increasing as CRCI is becoming better recognized as a toxicity that is associated with cancer therapy. A brief, noncomprehensive literature title search in PubMed of "cancer" and "cognitive function" or "cognitive dysfunction" or "cognitive impairment" demonstrates a rapidly increasing trend as shown in Fig. 11.1. The first citation using these criteria was identified in 1994 and focused on lung cancer [9]. Since then, research has expanded to focus primarily on breast cancer but also to include gynecologic, head and neck, prostate, testicular, and colorectal cancers. Over time, the research has expanded to consider animal models and structural and imaging studies and to address methodological and measurement

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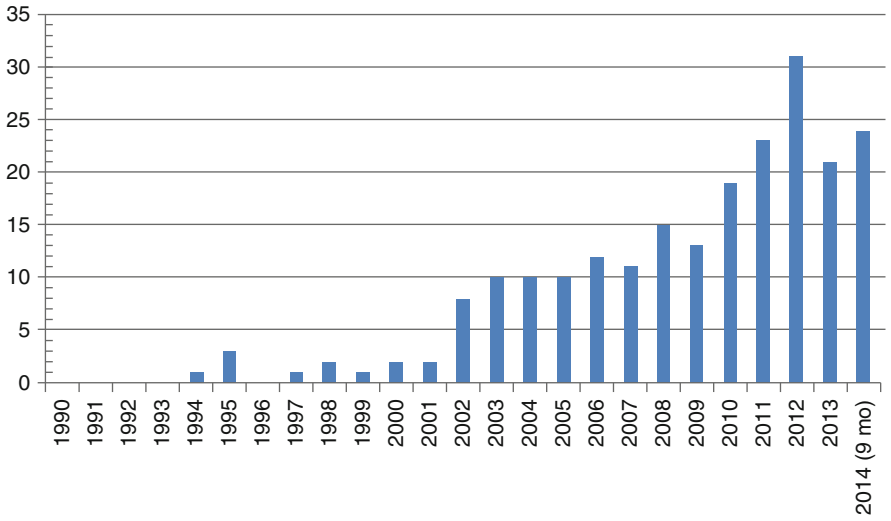

Fig. 11.1 Increasing research interest in cognitive function and cancer

issues as well as interventions for CRCI. Unfortunately, little consensus has been reached in the field despite recent organized attempts to standardize the field of research.

The incidence and duration of CRCI varies considerably from study to study and across diseases, with estimates that range from 0 % to nearly 70 % cancer patients being affected [10]. The actual incidence rate is difficult to identify due to the lack of sensitivity of many tests, the variable study designs used (e.g., cross-sectional or longitudinal, with or without a control group), a range of instruments used to measure cognitive functions, and the variety of definitions of what is determined to be an impairment on those scales [1]. In general, studies investigating CRCI have struggled with design and methodology issues that have limited progress. In addition to the known issues of confounding factors that can impact cognitive function, research in cancer is challenged with issues of sample size, defining an appropriate control group for comparison and defining an appropriate measurement tool or instrument [11].

11.2 Evidence

11.2.1 Tools and Instruments in CRCI

A number of meta-analyses and reviews [3, 12] have identified more than 30 tools and instruments assessing a variety of domains of cognitive function, demonstrating the disparate aspects of measurement of the overall concept of "cognitive function" and partially explaining why so many studies have found inconsistent results (Table 11.1).

Table 11.1 Sample of instruments used to date to assess cognitive function in cancer [3, 5, 10, 18, 27, 30]

Domain	Instrument measuring cognitive function	Patient-reported instrument
General cognitive function	CLOX test High Sensitivity Cognitive Screen (HSCS) Exit 25 test HeadMinder Cognitive Stability Index Mini Mental State Exam (MMSE) Hopkins Verbal Learning Test-Revised (HVLT-R) Trails A and B test Finger tapping test Cognitive Drug Research Computerized Cognitive Assessment Digit Span Test Revised Rey-Osterrieth Complex Figure Test (ROCFT) Neurosensory Center Comprehensive Examination for Aphasia F-A-S subtest California Verbal Learning Test-II (CVLT) Cog State Weschler Memory Scale (WMS) Weschler Adult Intelligence Scale (WAIS) Cantab Cognition CogHealth	Patient assessment of Own Functioning (FAP) Cognitive Failures Questionnaire Questionnaire of Experienced Deficits of Attention Perceived Cognition Questionnaire Functional Assessment of Cancer Therapy – Cognition (FACT-Cog) Perceived Health Scale – Cognitive subscale
Executive function	Fepsy Finger Tapping Grooved Pegboard Thumb Finger Sequencing Booklet Category Test HSCS self-regulation subtest Stroop Color and Word Test Trail Making Test (TMT)-Part B WAIS similarities subtest Controlled Word Association Test (COWA) WAIS-Revised/Similarities	EORTC-Cognitive item
Memory	Rey Auditory Verbal Learning Test (RAVLT) TMT Rey Complex Figure Copy test (RCFT) RCFT recall; RCFT delayed recall WMS recall Visual reproduction Verbal memory subtest of the Barcelona test Benton Visual Retention Test California Visual Learning Test (CVLT) Verbal Selective Reminding Test (VSRT)-Delayed recall Nonverbal Selective Reminding Test (NVSRT)-Delayed recall Groeninger Intelligence Scale MMSE WAIS Weschler Memory Scale (WMS) visual reproduction subtest	

(continued)

Table 11.1 (continued)

Verbal function and language	WAIS-III C WMS logical memory subtest Boston Naming Test Word fluency test Luria Memory Words Test Controlled Oral Word Association Test (COWAT) HSCS language subtest CVLT HSCS memory subtest RAVLT	
Construction	Block Design RCFT Copy	
Concept and reasoning	Wisconsin Card Sorting Test Arithmetic test	
Motor function	Grooved Pegboard Halstead-Reitan Neuropsychological Battery finger tapping subtest HSCS psychomotor subtest Fepsy Finger tapping Grip strength	
Perception/ recognition	Benton Faces Letter Cancelation CVLT RAVLT Hopkins Verbal Learning Test (HVLT) Rey 15-Item Test WMS verbal memory Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) immediate memory VRST short term RBANS delayed memory WMS delayed recall Verbal Selective Reminding Test – delayed recall WMS visual memory Visual reproduction II Family pictures II ROCFT recognition Visual association	
Processing speed	Fepsy Binary choice subtest Fepsy Visual reaction subtest Fepsy Visual searching subtest Paced Auditory Serial Addition Test TMT-Part A WAIS digit symbol subtest	
Visuospatial skills	HSCS spatial subset RCFT copy WAIS-R block design subtest	

Table 11.1 (continued)

Orientation/ attention	HSCS attention subset WAIS digit span subset WAIS special span subtest WAIS-revised/arithmetic Intra-Extra Dimensional Set Shift Digit span test TMT Letter Number Sequencing Useful field of view test Reading Span Test Timed Instrumental Activities of Daily Living WAIS III – symbol search Stroop Digit Symbol Cognitive Performance Test D2 Test Fepsy Binary Choice Fepsy Visual Searching Fepsy Visual Reaction Paced Auditory Serial Addition Test Symbol search Spatial Span Attention CR/Attention RT TMT - B Wisconsin Card Sorting Test Tower of London Consonant Trigrams Boston Naming Test WAIS Wide Range Achievement Test-Reading RBANS language Block design RBANS visuospatial	

There is a lack of standardization across research trials, and there is no instrument designed specifically to measure CRCI. Instead, CRCI is measured by tools that have been developed for issues such as head trauma [13, 14], psychiatric issues [15], dementia [16], and other health concerns that are likely quite different from those experienced by cancer patients. Additionally, cognitive function may be measured by memory and attention in one study but measured as response time and verbal abilities in another, so the research reports quite different domains of the same overall construct, which may not all be affected in the same manner. The domains are also not measured uniformly across trials. Memory may be evaluated with the California Verbal Learning Test (CVLT) in one study but then may be

evaluated using various subtests of the Weschler Memory Scale in another, making direct comparisons between trials difficult [12, 13]. In 2006, Vardy and colleagues demonstrated the variability in assessment of cognitive function using several instruments, including the CogHealth, HeadMinder, and the High Sensitivity Cognitive Screen (HSCS) tests, which found that 26 %, 55 %, and 30 % of patients in the same sample, respectively, experienced cognitive impairment simply depending on which instrument was used [17]. Other studies have demonstrated the lack of sensitivity of a variety of tests for the assessment of cancer-related cognitive function, despite those tests being sensitive, validated, and reproducible in the diseases or conditions for which they were developed [18, 19].

The International Cognition and Cancer Task Force was established in 2006 by several leading scientists in the field to address issues of assessment, study design and methodology, and the prevention and management of CRCI [20]. In 2011, this task force recommended for Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), and the Benton Controlled Oral Word Association (COWA) of the Multilingual Aphasia Examination to be used to study CRCI. These instruments measure the cognitive domains of learning and memory, executive function, and processing speed and were selected as recommended instruments because they met the task force criteria of (1) being an objective measure; (2) measuring the domains of learning and memory, processing speed, or executive function; (3) having adequate sensitivity to measure the domain; (4) having adequate psychometric properties; and (5) being frequently used in the study of CRCI [20]. While harmonization is certainly needed, there remains a need for appropriate instrument development and instrument selection in research of CRCI, as none of the recommended instruments were developed for this purpose.

The HVLT-R was developed to measure abnormal forgetfulness in the domain of verbal memory [21]. The HVLT-R takes approximately 30 min to complete (5–10 min assessment + 25 min delay). It has been shown to be sensitive to dementia. The test is available in the public domain. In studies of lung cancer, the HVLT-R detected a decline in cognitive function among approximately 20 % of patients treated with prophylactic cranial irradiation [22]. Differences in cognitive function were found in a study of breast cancer patients receiving erythropoietin using the HSCS, but no significant differences were detected from the HVLT-R [23]. In a study of newly diagnosed glioblastoma, the HVLT-R detected a 60 % rate of cognitive impairment [24]. A recent meta-analysis of CRCI did not identify any studies that included the HVLT or HVLT-R [3]. The HVLT was also not identified in studies included in a meta-analysis evaluating the effect size of instruments to study cognitive function in cancer patients [18].

The TMT was developed in the mid-twentieth century to assess brain damage [25]. The respondent draws a line to connect a series of 25 circles as quickly as possible. In Part A of the test, the circles are numbered 1–25 and they must be connected in numeric order. In Part B, the circles contain letters (A–L) or numbers (1–13), which must be connected alternating from letter to number and both in ascending order. The score is based on the time needed to complete. It has shown to be sensitive to both dementia, cerebrovascular disease, and Alzheimer's disease [26]. Despite its ability to detect

subtle cognitive changes, the TMT was found to have a small effect size in a meta-analysis of tools evaluating cognitive function in breast cancer patients [18]. In a study of colon cancer patients, the TMT detected no significant change over time (pre-chemotherapy through the post-chemotherapy or 6-month follow-up assessments) [27]. A longitudinal study of breast cancer patients found no significant differences using the TMT, but they did find significant differences using the HSCS when comparing cancer patients to controls [28]. A second study of breast cancer patients found no differences with the TMT-Part A, but that participants performed significantly worse before chemotherapy than during treatment on the TMT-Part B [29]. Other breast cancer studies have found no differences over time pre- to post-chemotherapy [30]. The TMT was also used to evaluate cognitive change over time in an ovarian cancer patient population; stable or improved scores (not significantly different) were found from baseline to the treatment period or following chemotherapy [31]. In a study evaluating cytokine levels of patients with leukemia, the TMT-Part B performance was found to be lower among those with higher levels of circulating IL-6 [32].

The COWA (also termed the FAS test in some studies, although the Benton set is most commonly used) is a verbal fluency test within the Multilingual Aphasia Examination that can be administered within 5–10 min [33]. The administrator provides a letter of the alphabet, and the respondent is to provide as many words as possible that begin with that letter within a one-minute time period [34]. It is scored by counting the number of words identified by the respondent. It was originally developed for patients with focal brain lesions and has been found to discriminate in studies of attention deficit and hyperactivity disorder, attention deficit disorder, amnesia, Huntington's disease, children with learning disabilities, and adults and children with head injuries [33]. In cancer research, one study found no differences in COWA test results with glioblastoma patients versus non-glioblastoma controls [35]. A study comparing pre-chemotherapy to short- and long-term follow-up time points among women receiving adjuvant treatment for breast cancer found no significant differences over time using the COWA, but significant differences were found using the Block Design, Booklet Category Test, Digit Symbol Test, Verbal Selective Reminding Test Long-Term Storage, and Nonverbal Selective Reminding Test Long-Term Storage at the short- but not long-term follow-up [30]. In a study comparing breast cancer patients to controls, COWA scores were significantly different, but the effect sizes were small [36]. Another longitudinal study in breast cancer demonstrated 5 % of patients experience cognitive decline over time using the COWA [37].

While each of the tests recommended by the Task Force met their stated criteria, none were developed specifically for the concerns of cancer patients. The selection of an appropriate measurement tool in any study must further be based on factors such as its ability to distinguish between those who are affected by CRCI and those who are not, the sensitivity of the test to detect CRCI, and the availability of parallel forms for prospective or longitudinal studies [18]. While the Task Force guidelines are an important first step to standardize the field and to produce criteria that may reduce the use of tests with little sensitivity that has troubled prior work, scientists must still thoughtfully select the instrument most appropriate to the study question and population of interest.

Patient self-report measures are useful for the impact of function on patient perspectives but cannot directly measure the cognitive function of individuals. This does not negate their importance in any way, as the most important aspect of toxicity to understand is the impact on individual patients, their quality of life, and functional abilities. Unlike the objective instruments discussed above, there are self-reported measures for cognitive function that were developed specifically for the cancer patient (e.g., EORTC-QLC C30 cognitive subscale and the FACT-Cog). The EORTC cognitive subscale contains only two items for cognitive function (memory and concentration, respectively) in the cognitive domain [38], limiting its use for studies focused on cognitive function. It has also been shown to perform poorly as a stand-alone subscale [39]. The development and psychometric properties of the FACT-Cog are available [40], and work has been published on the translation of the FACT-Cog for use in non-American populations [17, 41]. A new version of the scale is in development but has yet to be published.

Thus, despite the increased interest and recognition of this issue, there currently is no standard approach to measure cognitive function in the cancer patient receiving chemotherapy. The underlying problem is still poorly understood, and no validated tools have been developed to measure the cognitive changes that occur specifically in cancer populations.

Despite the lack of validated instruments to measure CRCI and the variability in outcomes across studies, many studies are able to identify a subset of patients who experience cognitive decline in various domains. Individual studies report incidence rates of CRCI ranging from 0 % to nearly 70 % [10]. Meta-analyses of cognitive function in the cancer patient have tried to better understand this concern by pooling results across cognitive domains.

A meta-analysis of 13 studies that were published through 2010 found that executive function, memory, verbal function, and language skills were significantly impacted but that all had very small effect sizes [3]. Neither patient age nor time since treatment discontinuation was a contributing factor to these declines. This study was limited to studies comparing patients receiving chemotherapy compared with a control group, patients over the age of 21, and studies that provided calculated effect sizes and that had a primary aim of studying cognitive function. The eligible studies were primarily breast cancer trials, but leukemia, testicular cancer, and lymphoma studies were also included in the analysis.

A larger meta-analysis was conducted of 44 studies that were published through January 2011 [10]. This meta-analysis included more studies due to broader eligibility criteria. All studies of chemotherapy and cognitive function that had a control group and reported a mean value of the cognitive assessment with either a cross-sectional or longitudinal design were included. This study computed a Hedge's *g* for each of the studies; nearly three quarters of the eligible studies were from breast cancer populations. This meta-analysis found few statistically significant effects (visual memory and visual recall significantly improved and only selective attention declined versus controls), and the effects were of small size. This could be largely due to the heterogeneity of studies washing out any potential effect seen in a more selective subgroup of studies. In a subset analysis of cross-sectional trials, there

were more impairments identified versus controls (significant differences found for the domains of memory, immediate free recall, delayed memory, delayed recognition, verbal memory, verbal immediate free recall, verbal delayed free recall, verbal delayed recognition, selective attention, and capacity of attention) [10]. When limited to longitudinal studies, improvements in cognitive function after chemotherapy were identified for many of the domains studied (i.e., immediate free recall, verbal immediate free recall, visual immediate free recall, visual delayed memory, focused attention, capacity of attention, and verbal abilities all significantly improved over time).

An additional meta-analysis was conducted of 17 studies in breast cancer published through June 2011 that found significant declines in verbal ability and visuospatial ability for breast cancer patients receiving chemotherapy compared to controls, but the effect sizes were small [42]. These declines were also not moderated by a number of factors that had been suspected of influencing cognitive function, such as age, time since treatment, education, or endocrine therapy. Thus, even across recent meta-analyses for similar time periods, the results remain inconsistent and additional research is needed.

11.2.2 Neuroimaging in CRCI

In recent years, researchers have shown greater interest to utilize novel neuroimaging technology to define structural, functional, and molecular changes to understand patterns of brain abnormalities associated with CRCI in breast cancer survivors. These studies use neuroimaging techniques combine with detailed cognitive assessment to evaluate the changes associated with chemotherapy. Quite a few of studies showed evidence of alterations on neuroimaging that may explain the cognitive impairment in patients exposed to chemotherapy [43–65].

Several structural magnetic resonance imaging (MRI) studies have utilized voxel-based morphometry (VBM) to assess regional abnormalities in the brain associated with chemotherapy [43, 44, 46–51]. *Vertebral Motion Analysis (*VMA) is a fully automated structural neuroimaging technique used for quantitatively evaluation of the brain to detect the differences in regional volume and density. A prospective, longitudinal study of 44 patients included 17 breast cancer patients treated with systemic chemotherapy, 12 breast cancer patients without chemotherapy and 18 healthy controls. At baseline, no between-group structural brain differences were observed prior to initiation of systemic chemotherapy. One month following chemotherapy, patients had diffuse loss of gray matter volume and density. At 1-year follow-up, a partial gray matter recovery was observed with alterations persisting predominantly in frontal and temporal regions. This trend was not observed in patients who received antiestrogen treatment without systemic chemotherapy and healthy control.

Other prospective VBM analyses [43, 46] also showed diffuse loss of gray matter volume and density shortly after systemic chemotherapy. These gray matter alterations partially recover overtime after chemotherapy. At 1 year, close to half of the

regions with gray matter volume loss had resolved [43]. This phenomenon correlates with the severity of cognitive impairment in cancer patients, worst during or soon after chemotherapy and gradual improvement in cognitive function with partial recovery overtime [43, 44]. A study found that gray matter density was directly related to cognitive performance in the domains of processing speed, working memory, and visual memory [48]. The recovery from chemotherapy overtime was partial and not a complete return to baseline. Long-term irreversible abnormalities related to chemotherapy persistent in the gray matter distributed in frontotemporal regions [43, 44, 49]. Moreover, studies have demonstrated residual gray matter deficits in the chemotherapy-treated breast cancer patients, even beyond a decade after adjuvant therapy completion [48–50]. The total reduction of gray matter volume associated with chemotherapy was comparable to almost 4 years of age-related decline in gray matter volume [48]. These findings may provide evidence to explain the subtle but clinically relevant residual cognitive deficit in a subset of breast cancer survivors.

Diffusion tensor MRI (DTI) is capable of detecting subtle changes in the microstructure of white matter fiber tracts. DTI has the sensitivity required to quantify microstructural changes in white matter integrity related to CRCI in the breast cancer population. DTI measures the diffusion of water molecules along fiber tracts, reflecting white matter local microstructure and anatomy. The main parameters are fractional anisotropy (FA) reflecting the directionality of diffusion and mean diffusivity (MD) describing the amount of diffusion within a voxel. Intact white matter tissue is thought to be characterized by high FA and low MD [66].

A cross-sectional, pilot study [55] investigated the effect of chemotherapy on white matter in the genu of the corpus callosum in breast cancer patients compared to healthy controls. Compared to controls, patients treated with chemotherapy had both slower processing speed and lower FA in the corpus callosum. In this region-of-interest analysis, only corpus callosum was selected for DTI parameters of white matter integrity. Subsequently, whole-brain DTI studies showed similar evidence that chemotherapy was associated with abnormal microstructure in white matter indicating loss of integrity. Furthermore, a relationship was identified between white matter alteration and cognitive decline in chemotherapy-treated breast cancer patients [49, 50, 55–57]. The quantitative FA changes in frontal, temporal, and parietal white matter tracts, including the superior and inferior longitudinal fasciculus, directly correlated with neuropsychological test scores in the cognitive domains of memory, attention, and processing speed. The subjective self-reported cognitive complaints also correlated with FA changes in frontal and parietal white matter regions. Moreover, breast cancer patients with CRCI showed a greater degree of white matter injury [56, 57]. Long-term changes in white matter microstructure were also observed in breast cancer patients 10 years after high-dose chemotherapy. In the chemotherapy group, observed DTI abnormalities were localized close to regions with reduced gray matter volume and density [49, 50].

A longitudinal whole-brain study [56] compared DTI measures in white matter taken before and 3–4 months after chemotherapy with detailed cognitive assessment. This study also included breast cancer patients not exposed to chemotherapy

and healthy controls which underwent the same assessment at matched intervals. No baseline differences between the three groups were observed in FA values or cognitive testing score. After chemotherapy, both FA values and cognitive test scores decreased compared to baseline. No changes were observed in either control groups at same time interval. These findings suggest that the longitudinal changes in white matter microstructure are specific to chemotherapy exposure and not related to cancer or antiestrogen therapy. A larger cross-sectional study [54] in breast cancer survivors (average >20 years) found a decline in white matter microstructural integrity with longer time since chemotherapy.

In CRCI research, very little evidence has been reported on differences in specific chemotherapy, chemotherapy regimen, or the relationship between dose and cognitive outcomes. A study compared high-dose versus conventional-dose chemotherapy regimen in addition to radiation only and healthy control [50]. A lower global white matter integrity and lower cognitive test score was found in the high-dose chemotherapy group compared to the conventional-dose group. In the conventional-dose chemotherapy group, a focal loss of white matter integrity was found predominantly in the frontal brain region [50, 57]. These findings suggest an association between high-dose chemotherapy and worse cognitive functioning, long-term lower local gray matter volume, lower white matter integrity, and lower axonal function, whereas the effects of conventional-dose chemotherapy were less pronounced and less widespread. This suggests that even ≥10-year post-high dose treatment, patients may experience worse cognitive and structural brain outcomes than those treated with conventional-dose chemotherapy [50].

Functional MRI (fMRI) and positron emission tomography (PET) studies are functional neuroimaging techniques that may contribute to detect differences in brain function even without a clear structural damage. PET records the distribution of radioactive tracers to assess brain metabolism, whereas fMRI relies on differences in the magnetic properties of oxygenated and deoxygenated hemoglobin varying with the metabolic demands of the brain tissue. Functional studies measure areas of brain activation during selected tasks to target cognitive domains previously identified in neuropsychological assessment [67, 68]. In functional brain research, fMRI has become the preferred method in recent years in view of its higher resolution and the absence of radioactive exposure [68].

In a functional imaging study [60], PET showed increased activation of left inferior frontal cortex, during verbal memory task, in the chemotherapy-treated group compared to the not-treated breast cancer survivors. This increased activation during the verbal memory task was interpreted by the study team as compensatory response to overcome the underlying chemotherapy-induced deficit [60]. A case study [61] utilized fMRI to investigate a monozygotic twin (chemotherapy-treated twin compared to the healthy, untreated twin). The chemotherapy-treated twin had substantially more self-reported cognitive complaints. Although the task performance scores were similar, the chemotherapy treated had broader task activation of bilateral frontal and parietal regions compared to the untreated. Again, the authors interpret this pattern of increased activation as evidence of compensatory strategy (increase in effort to recruit more circuitry) to maintain performance.

More recently, fMRI studies reported significant decrease in brain activation during multitasking in the chemotherapy-treated breast cancer patients [47, 49, 52, 58, 59]. Specific fMRI findings include task-specific decreased activation in the prefrontal and parietal regions during tasks of executive function [47, 49, 52, 58, 59], and decreased activation in the parahippocampal gyrus was observed with a memory-encoding paradigm and generalized decreased activation of lateral posterior parietal cortex consistent with decreased attention processing [49, 59]. Interestingly, chemotherapy-induced loss in gray matter density [47, 49, 53, 59] and/or white matter microstructural [49] overlapped with some of the brain regions with altered pattern of activation on fMRI. Therefore, the significant decrease in brain activation during multitasking may be associated with chemotherapy-induced decline in quality of brain tissue. In neurocognitive assessments, chemotherapy-treated patients performed significantly worse than the control group(s) [47, 49, 53, 58, 59]. The subjective self-reported cognitive complaints also correlated significantly to decreases in multitasking-related brain activation [52, 58]. Conversely, an increased activation of the dorsolateral region of the prefrontal cortex was associated with improved task performance in chemotherapy-treated patients [59]. These findings were interpreted as specific regional impairment in brain function related to CRCI.

Several fMRI studies reported increase in bilateral frontoparietal brain activation in breast cancer patients not (yet) treated with chemotherapy compared to healthy control [53, 62, 64], which raised the concern about possible early deficiency in brain function in breast cancer associated with other variables (e.g., fatigue, other treatment(s), response to illness). These functional alterations in frontoparietal region resemble the findings associated with normal aging that is evident in older adults [64]. The authors interpreted the increase brain activation as recruitment of additional circuitry to compensate the functional insufficiency [53, 62, 64] possibly due to fatigue [64]. A prospective study in resting-state fMRI of 65 patients reported greater fatigue in pre-chemotherapy group compared to radiation therapy-only and health control group. The pre-chemotherapy group showed greater frontoparietal executive network variance on fMRI than the radiation therapy-only group. The authors interpreted this greater frontoparietal variance in the executive network as a predictor of neural inefficiency that is more likely to lead to future CRCI [65]. Another study [63] on resting-state fMRI displayed altered network organization in frontal, striatal, and temporal areas in chemotherapy-exposed breast cancer patients compared to healthy controls. The breast cancer group had greater self-reported complaints of decline in executive function and memory. These alterations in resting-state network properties suggest a decrease in processing efficiency. The functional inefficiency may lead to greater effort and perceived challenge for everyday cognitive demands. The authors note that several of the specific alterations observed in the study resemble findings reported in association with normal aging [63].

More complex findings were reported in a prospective fMRI evaluation of breast cancer patients at matched intervals (at baseline/pre-chemotherapy, 1 month and 1 year post-chemotherapy) [53]. At baseline, breast cancer patients (not treated and

not yet treated with chemotherapy) had increased activation in frontal region bilaterally compared to healthy controls. At 1 month after chemotherapy, a decrease activation was observed in the previously mentioned area of activation. At 1 year after chemotherapy, increased activation to baseline level was observed in the frontal brain regions, accompanied by overlapping of a persistent gray matter volume decrease [53]. These findings were interpreted by some authors as compensatory activation, but early cognitive compromise specifically related to cancer could not be excluded. In contrast, a similar longitudinal fMRI study [52] did not find a pre-chemotherapy difference in task-related brain activation among the three groups. Moreover, no structural differences in gray matter volume [46] or white matter microstructure [56] at baseline were reported in the prior VMA or DTI studies; therefore, the observed pre-chemotherapy increase in brain activation is more likely related to cognitive strategies (compensatory activation) rather than a reflection of brain pathology [52].

DTI studies [49, 50, 56, 57] suggest that brain white matter tract may be particularly sensitive to injury after chemotherapy exposure. These microstructural damages could reduce the efficiency of signal transmission and result in decreased activation to the involved brain regions (reduced network connectivity). A multimodality MRI study [49] combined VMA, DTI, fMRI, single-voxel proton MR spectroscopy, and neuropsychological testing. 1H-MRS in the left centrum semiovale showed a reduction of N-acetylasparate (NAA)/creatine (Cr) ratio in chemotherapy-treated patients, a marker of axonal injury. DTI parameters correlated with 1H-MRS NAA/Cr ratio in the chemotherapy group. These results suggest that chemotherapy is associated with long-term damage to white matter (presumably from axonal degeneration and demyelination). In another multimodal MRI study [47], DNA damage in the peripheral lymphocyte (by modified alkaline Comet assay) was higher in the chemotherapy-treated group compared to healthy control. Increased DNA damage in this study was also associated with reduced gray matter density and decreased brain region activation on fMRI. Collectively, the data suggest that chemotherapy-associated injuries interfere with brain activation during complex mental operations and that this reduction in brain activity is related to CRCI [52].

Available neuroimaging studies provide evidence to support chemotherapy-induced gray matter atrophy [43, 44, 46–51] and white matter microstructural damage [49, 50, 55–57]. Abnormalities in white matter microstructure in the frontal brain region have been consistently reported in the DTI studies [49, 50, 56, 57]. Interestingly, longitudinal VBM studies [44, 46, 53] also demonstrated reduced gray matter in frontal regions in chemotherapy-treated patients, while no changes were found in controls or patients who received hormone treatment but not chemotherapy. These findings are alien with fMRI studies that also report differences in brain activation patterns after chemotherapy in the frontal cortex [47, 49, 52, 58, 59]. This relationship between gray matter reduction in the frontal lobes with the decreased performance on executive function, working memory, and visual memory may help support the neurobiology of CRCI [43, 44, 46].

In summary, structural, functional, and molecular neuroimaging has the potential to help define the neurobiology of CRCI. Prospective studies designed with larger

sample sizes and more time intervals since chemotherapy will be needed to compare specific subgroups in terms of age, stage, comorbid conditions, menstrual status, and treatment (hormone therapy alone, specific chemotherapy regimen/dosing, or in combination) to help distinguish specific variables that may attribute to cognitive decline in cancer survivors. Moreover, future neuroimaging studies should aim to identify potential risk factors and better characterize the natural course of CRCI.

11.3 Ongoing Research

There are a number of efforts to address the gaps in knowledge regarding CRCI. The Gynecologic Oncology Group (GOG) recently completed GOG-0256, a prospective trial of 220 ovarian cancer patients in which cognitive function was measured at four time points by self-reported and web-based cognitive tests from baseline (pre-chemotherapy) to 6 months of post-treatment discontinuation. The final results were published in 2015 [69]. There are a number of other studies not yet completed that are reported at www.clinicaltrials.gov. A subset of these ongoing studies is summarized in Table 11.2.

An advanced search of clinicaltrials.gov using the keyword "cognitive" with "cancer" as the condition term found 184 open studies. While this general search will overestimate the body of research by identifying studies that are not CRCI specifically (e.g., the search also captured radiation therapy studies or brain tumor studies or studies that include cognitive function as secondary or exploratory endpoints), this does represent the growing interest and scientific work related to cognitive function in cancer and CRCI. Of all open studies, 140 (76.1 %) were interventional trials. This increased interest is compared to 244 studies that are reported as being closed to accrual. Of those earlier trials, 170 (69.7 %) were interventional designs. Of the total 428 studies, the majority was registered at clinicaltrials.gov from the USA ($n=276$, 64.5 %), Europe ($n=97$, 22.7 %), and Canada ($n=36$, 8.4 %). Of ongoing trials, there is more international representation with the US institutions conducting approximately half of the registered research: 52.1 % of all interventional studies and 54.3 % overall.

Several neuroimaging studies are also being conducted (e.g., City of Hope Medical Center, Brain Functional MRI in Older Women with Breast Cancer, NCT01992432), but there remain gaps in the knowledge of the relationship between the changes in brain structure and cognitive issues. Despite this gap in knowledge of the physiologic changes in CRCI, much of the current work is interventional, designed to improve the condition rather than to better understand it. The interventional research that is currently ongoing is primarily focused on behavioral interventions to treat cognitive decline. A study in France was recorded in the clinical trial registry, randomizing patients with prior cancer therapy complaining of cognitive

Table 11.2 Selected examples of ongoing clinical trials of cognitive function and cancer

Trial identifier	Study title	Summary/purpose of study
NCT01382082 [80]	Assessment of Cognitive Function in Breast Cancer and Lymphoma Patients Receiving Chemotherapy (CANTAB)	"This is a longitudinal observational study of cognitive function in breast cancer and lymphoma patients receiving chemotherapy to better understand the prevalence of cognitive difficulties (i.e., problems with memory, executive function, and attention) in these populations"
NCT00579072 [81]	The Impact of Androgen Ablation Therapy on Cognitive Functioning and Functional Status in Men With Prostate Cancer Age 65 and Older	"The purpose of this study is to find out if therapy with hormones change a person's thinking abilities"
NCT01788618 [82]	Cancer and Disorders of Cognitive Functions and Quality of Life: "Cognitive Rehabilitation in Patients Suffering From Cancer and Treated With Chemotherapy"	"(This) study aims to measure the impact of cognitive rehabilitation workshops on the development of cognitive functions and quality of life of patients expressing a cognitive complaint"
NCT01238120 [72]	The Effects of Physical Activity and Low-Dose Ibuprofen on Cognitive Function in Cancer Patients	"A combination of low-dose ibuprofen along with a structured home-based walking and progressive resistance exercise program, EXCAP, will be effective in reducing cognitive difficulties among cancer patients receiving chemotherapy"
NCT00756132 [70]	Using Bio Markers to Predict Disease Recurrence and Cognitive Function in High Risk Breast Cancer (Cyto-Cog)	"This longitudinal study evaluates the relation of cytokines to decreased thinking abilities and to disease outcome over time. Results of this study may help develop interventions to prevent or minimize cognitive decline and identify women who are at high risk for recurrence, and such information could be used in treatment decisions and in the development of new treatment options"
NCT01596439 [83]	A Prospective Study to Evaluate the Effect of Systemic Adjuvant Therapy on the Cognitive Function of Breast Cancer Patients	"The primary objective of this prospective pilot study is to examine the variation of cognitive function at various time-points in stage I-III breast cancer patients who have undergone or are undergoing adjuvant systemic therapy (chemotherapy and/or anti-hormonal therapy) and compare this to a group of healthy controls to evaluate if there is a difference"

(continued)

Table 11.2 (continued)

Trial identifier	Study title	Summary/purpose of study
NCT02162329 [71]	Effects of Meditation on Cognitive Function and Quality of Life	"The goal of this research study is to test Tibetan meditation as a therapy to teach cancer patients to change their brain functioning and to improve quality of life. Researchers want to compare the cancer patients' outcomes to people who have never had cancer"
NCT01540955 [78]	Cognitive Rehabilitation Group Intervention for Breast Cancer Survivors	"This study is designed to test the efficacy of a 5 week group-based cognitive rehabilitation intervention on improving cognitive complaints and test performance, in comparison to women who will receive the same intervention at a later time (wait-list control)"
NCT01983267 [84]	Cannabis-related Cognitive Impairment: Prospective Evaluation of Possible Influences in Cancer Patients During Active Oncology Treatment	"The main goal of the study is to evaluate prospectively the level of reduction in cognitive function of cancer patients who are on active oncology treatments and use cannabis, comparing to a group of patients without cannabis treatment. The second goal is to identify high-risk groups for cognitive impairment due to cannabis use"
NCT01597284 [85]	Oral Therapies in Oncology: Cognitive Function and Compliance	"The investigators propose to evaluate the compliance of oral cancer therapies, particularly the possible link between this observance and cognitive function of patients at initiation of treatment"
NCT01949376 [86]	Mild Cognitive Impairment in Breast Cancer Patients (HippoPCI)	"The purpose of this study is to improve our understanding of potential changes in size, shape and activity in some brain areas that can occur in women receiving different types of Breast Cancer therapy, and how these changes are related to the development of mild cognitive impairment as the result of these treatments"
NCT01641068 [87]	Memory and Thinking Skills Workshop in Improving Cognitive Rehabilitation in Gynecologic and Breast Cancer Survivors	"The purpose of this study is to examine thinking abilities, mood, and quality of life in cancer survivors before and after an 8-week group-based memory and thinking skills workshop"

Table 11.2 (continued)

Trial identifier	Study title	Summary/purpose of study
NCT01866813 [88]	Internet-Delivered Cognitive Training For Breast Cancer Survivors With Cognitive Complaints	"The aim of the proposed study is to investigate whether women treated for breast cancer who experience cognitive difficulties will profit from the Internet-based program Scientific Brain Training Pro with respect to: (1) attention, working memory, learning and recall, and executive function as assessed by standardized neuropsychological tests and (2,) self-reported cognitive difficulties in daily life as measured by questionnaires"

Available at www.clinicaltrials.gov

difficulties to one of three groups: web-based cognitive rehabilitation sessions, telephone follow-up, or to nine home exercise sessions [70]. This study status is unknown, however it was initially expected to complete enrollment in 2015. A study being conducted by the M.D. Anderson Cancer Center is designed to evaluate the effect of meditation on cognitive function among patients with breast cancer who experience cognitive complaints versus healthy controls [71]. The results of this study are not expected until at least 2017.

Research is ongoing combining behavioral with pharmacologic solutions to assess the efficacy of these interventions. For example, there is a randomized phase II study underway at the University of Rochester evaluating four different interventions for cancer patients experiencing cognitive difficulties (NCT01238120) [72]. Patients are randomized to ibuprofen alone, ibuprofen + exercise, placebo + exercise, or placebo alone. The study is designed to evaluate the impact of ibuprofen and/or exercise interventions on memory and on self-reported cognitive function, measured by the FACT-Cog. This study is expected to be completed in 2018.

While in general, it is better to prevent a problem than to treat a problem after it has occurred, prevention or risk reduction studies for CRCI are challenged by a number of logistical issues. This is likely the reason why very little research is focused on the prevention of cognitive decline among cancer patients receiving chemotherapy. Studies designed to treat the effects of cancer can be a smaller sample size than prevention or risk reduction studies, because all affected patients are enrolled, all patients are randomized to a treatment strategy or control group, and all patients' data can be analyzed. When conducting a prevention trial, many patients will be enrolled who will never experience the problem in the first place. When the incidence rate of a problem is low, such as for CRCI (which may be as low as 20 % in some tumors) [69], power analyses must be conducted to have statistical significance to either reduce the incidence rate or to demonstrate reduced severity among that subset of patients who will experience the problem. This results in very large sample sizes to attain the number of affected individuals for analysis. To address this and other limitations of prevention research strategies in CRCI, work is needed to identify those at greatest risk of developing cognitive problems. If these subsets

at highest risk can be identified, solutions can be directed at those most likely to need them, rather than to a broad population who may never need the intervention. As with all prevention or risk reduction strategies, balance must be made between potential risk and potential benefit. If the majority of the population has no chance of benefit, these trade-offs become more difficult to justify.

11.4 Solutions

Despite the limited evidence, there are several guideline documents in place for CRCI. ONS (Oncology Nursing Society) has conducted an evaluation of the evidence and has produced a guidance document as part of their Putting Evidence Into Practice® series entitled *Evidence-Based Interventions for Cancer and Cancer Treatment-Related Cognitive Impairment* [73]. The evaluation included a systematic literature review that identified 29 studies of interventions for CRCI [74]. Their work is updated on a regular basis and demonstrates that few interventions are currently supported by the evidence (Table 11.3). On the other hand, there is also no strong evidence showing that most interventions are ineffective; therefore, the effectiveness remains unknown, and there is a need for additional research for each of these interventions. The only intervention with sufficient evidence to consider it "likely" to be effective is group cognitive training.

However, the recommendation for group cognitive training does not identify a specific intervention but rather suggests a broad approach. ONS defines group cognitive training as "any intervention aimed at improving, maintaining, or restoring mental function through the repeated and structured practice of tasks which pose an inherent problem or mental challenge. Group cognitive training is provided to individuals in a group setting" [73]. However, the various strategies and cognitive training programs may not all be equally effective.

The evidence recommendation is based on three studies: one in high-grade glioma [75] and two studies in breast cancer [76, 77]. The first of these supporting trials was a small, 11-patient pilot study of glioma patients that involved ten 90-min holistic mnemonic training sessions [75]. The study was a pre–post design with patients serving as their own controls. While the raw number of impaired individuals was lower in the follow-up assessment, there were no significant differences between the pre- and post-intervention assessments, with the exception of verbal learning ($p = 0.04$). The primary limitation of the study was the small sample size, limiting the ability to detect differences. One breast cancer study was a small ($N = 82$), randomized three-arm trial [77]. In this study, patients were randomized to memory training (adapted from the Advanced Cognitive Training for Independent and Vital Elderly trial), processing speed training (using Insight program by Posit Science®), or a waitlist control. Each of the training interventions involved ten one-hour sessions delivered over 6–8 weeks to small groups (3–5 patients). The memory group demonstrated significant differences in memory versus the control group during, but not following, the intervention. The processing speed group demonstrated significant differences in processing speed versus the control group both during and

Table 11.3 2014 ONS recommendations regarding effectiveness of treatments for cancer treatment-related cognitive impairment [73, 74]

Likely to be effective
Group cognitive training programs
Effectiveness not established: insufficient evidence
Non-pharmacologic
Vitamin E
Exercise
Natural restorative environmental interventions
Multicomponent rehabilitative interventions
Mindfulness-based stress reduction
Individual cognitive training programs
Mind-body-spirit therapy/Qigong
Cognitive behavioral interventions
EEG biofeedback
Meditation
Pharmacologic
Dexmethylphenidate
Methylphenidate
Modafinil
Donezepil
Effectiveness not likely:
Gingko biloba
Not recommended for practice
Erythropoietin-stimulating agents (ESAs)

following the intervention. While there is evidence suggesting that these approaches may have value, additional studies are needed.

One recently completed study, NCT01540955 (Cognitive Rehabilitation Group Intervention for Breast Cancer Survivors), utilized an intervention comprised of two-hour sessions, once a week for 5 weeks. A trained therapist targeted specific domains of cognitive functioning (e.g., memory, multitasking, attention), and participants completed tasks between the weekly sessions to improve cognitive function [78]. While this study did not utilize any of the approaches used in the studies supporting ONS recommendations, the study results, when available, may help clarify the role of group cognitive interventions via a more adequately powered and designed trial.

The LIVESTRONG Foundation produces an online resource for cancer survivors to help in the development of a survivorship care plan after completion of active cancer therapy [79]. This tool is tailored to the disease, treatment, and prognosis for individuals based on the clinical and demographic data each survivor enters in the tool. Part of the care plan for patients addresses the issue of CRCI. While limitations of research are noted, the care plan notes that research is investigating a number of medications (such as methylphenidate, modafinil, and antidepressants) as well as herbal interventions (such as ginkgo biloba). The care plan also notes that cognitive rehabilitation programs and memory training programs may be helpful for cognitive problems after chemotherapy. Lastly, the care plan points out the

importance of diet, exercise, and rest that may help one avoid fatigue (which can in turn increase cognitive problems) [79]. However, there is a lack of scientific evidence to make any solid recommendations for care. It remains unknown if these recommendations will reduce the impact of CRCI.

11.5 Future Directions

Research involving structural, functional, and molecular neuroimaging may help to identify potential risk factors and better characterize the natural course of CRCI. Improved instruments to identify and diagnose CRCI are needed. The increase in research and recognition of CRCI as an effect of chemotherapy has led to more strategic investigations in identifying, preventing, and treating these cognitive issues; however, little meaningful progress has been made that can improve patient outcomes. Additional research is needed to reduce the impact of cognitive decline among cancer patients treated with chemotherapy.

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Sleep Disorders

12

Ann M. Berger, Jennifer N. Miller, and Marcia Y. Shade

12.1 Problem: Sleep Disorders

Sleep disorders have been identified by experts and coded in The International Classification of Sleep Disorders (ICSD) [1]. This classification is the current primary diagnostic, epidemiological, and coding resource for clinicians and researchers in the field of sleep and arousal disorders and sleep medicine worldwide. The third edition of the ICSD (ICSD-3) sorts the sleep disorders into several categories, of which insomnia is the most common in the general population and in adults with cancer. Sleep-related breathing disorders and sleep-related movement disorders often occur in the general population, but little is known about their prevalence in adults with cancer.

Each sleep disorder in the ICSD-3 is described in detail. For adults with cancer, the published information includes: diagnostic criteria; essential and associated features; predisposing and precipitating factors; onset, course, and complications; and objective findings. Sleep disorders may be diagnosed during the diagnostic workup, treatment, or posttreatment phases of the cancer trajectory. Healthcare clinicians frequently encounter adults who report trouble falling asleep, staying asleep, early morning awakenings, and daytime dysfunction that occur comorbid with cancer. The term "sleep-wake disturbances" is used in reference to these symptoms when a sleep disorder has not been diagnosed [2].

The ICSD-3 divides insomnia into two major diagnostic categories with criteria that apply to patients with and without comorbidities: chronic insomnia disorder and short-term insomnia disorder. Prevalence rates of insomnia in adults with cancer have ranged from 25 to 69 % [3] compared to 8 to 18 % in the general

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population [4]. Prevalence rates of sleep-related breathing disorders, most commonly obstructive sleep apnea (OSA), have been estimated to be 2–5 % of women and 3–7 % of men in the general population [5], but no rates were found for OSA in adults with cancer. Sleep-related movement disorder, restless leg syndrome (RLS), is estimated at 5–10 % prevalence in European and North American population-based studies [1, 6]. The exact prevalence of periodic leg movement disorder (PLMD) in the general population is not known; no rates are reported for either RLS or PLMD in adults with cancer.

The current problem is that sleep-wake disturbances and sleep disorders that occur in cancer patients are underrecognized and undertreated in oncology and primary care settings. The occupational impact of poor quality and quantity of sleep in adults includes absenteeism, accidents, and low job satisfaction [7]. These consequences affect socioeconomic status: an important factor to 14 million US cancer survivors [8]. The impact of undertreatment on morbidity and mortality is drawing considerable attention as the number of cancer survivors increases worldwide.

The purpose of this chapter is to provide oncology and primary care clinicians (physicians, nurse practitioners, physician assistants, registered nurses, and other providers), as well as patients and their families, with knowledge related to the problem of sleep-wake disturbances and sleep disorders in patients with cancer. Content has been organized as current evidence, ongoing research, solutions, and future directions to advance resolution of, and reduce the negative consequences of this problem.

Insomnia is defined by the American Academy of Sleep Medicine (AASM) as persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity (7–9 h set aside to sleep) and circumstances for sleep and results in some form of daytime impairment [1]. OSA is defined by AASM as characterized by repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction occurring during sleep. Sleep-related movement disorders are defined by AASM as conditions characterized by relatively simple, usually stereotyped, movements that disturb sleep or its onset (see Table 12.1 for definitions and presenting symptoms of common sleep disorders in adults).

12.2 Current Evidence

Underdiagnosis of sleep-wake disturbances and sleep disorders is a problem that can be linked directly to a lack of screening and assessment in clinical settings. Sleep-related screenings can be included in a brief intake health history and medication review. The release of the Pan-Canadian practice guideline is a promising advancement to improve screening, assessment, treatment, and health outcomes of sleep disturbances in adults with cancer [9], but consensus to disseminate and adopt this or other guidelines is the next challenge. No instrument with reliability and validity established in adults with cancer is used routinely to screen for sleep-wake

Table 12.1 Common sleep disorders in adults

Sleep disorder	Definition	Presenting symptom
Insomnia	Difficulty initiating or maintaining sleep that causes significant daytime impairment or distress for 3 months or more	Patient complains of difficulty falling asleep, staying asleep, or early morning awakening that impairs daytime function
Obstructive sleep apnea-hypopnea syndrome	Recurrent episodes of partial or complete upper airway obstruction despite ongoing respiratory effort during sleep	Patient wakes with breath-holding, gasping, or choking; bed partner reports habitual snoring
Narcolepsy	Uncontrollable sleepiness and intermittent signs of rapid eye movement sleep that interrupt normal wakefulness	Patient reports repeated episodes of need to sleep and suddenly falling asleep during usual daytime activities
Restless leg syndrome	Urge to move legs and unpleasant and uncomfortable sensations in legs at night that are relieved by movement of limbs	Patient describes feelings of creeping, tingling, or cramping pain in legs that is worse when patient is lying down
Periodic limb movement disorder	Periodic or random leg kicking or arm movements during sleep	Bed partner reports kicking or arm movements by patient during sleep
Circadian rhythm disorder	Advanced or delayed major sleep episode in relation to desired clock time that results in undesired insomnia or sleepiness	Patient reports inability to fall asleep or awaken relative to conventional sleep-wake times
Parasomnias	Undesirable physical events or behaviors that occur during sleep	Bed partner reports behaviors by patient such as sleepwalking, sleep talking, or sleep terrors
Hypersomnias	Constant or recurrent episodes of extreme sleepiness and lapses into sleep	Patient reports excess sleeping at night plus long naps during the day and still feels sleepy

Note. Based on information from AASM, 2014

disturbances comorbid with cancer in primary care or oncology clinics. The Pan-Canadian practice guideline suggests a two-step screening process: a yes/no reply to a question about the occurrence of a sleep problem, followed by two questions that are designed to determine the relationship between the sleep problem and daily functioning.

The Pan-Canadian guideline recommends that those who screen positive for insomnia undergo further assessment to identify the presence of signs and symptoms of sleep disturbances. The assessment is combined with a sleep diary such as the Consensus Sleep Diary [10] and the Insomnia Severity Index [11]. Objective actigraph data may be collected to complement subjective data.

When excessive daytime sleepiness, measured by the Epworth Sleepiness Scale (ESS) [12], is detected, OSA is suspected and immediate referral to a sleep center for polysomnography (PSG) is recommended. The STOP [13], STOP Bang [13], or Berlin [14] OSA screening tools may be preferable to the ESS because of higher

sensitivity and inclusion of biomarkers (i.e., body mass index, blood pressure) in addition to age, gender, excessive snoring, witnessed sleep apnea, or gasping for breath [15].

PLMD screening is performed by asking the patient and bed partner about leg kicking or arm movements during sleep, and if the screen is positive, PSG is recommended [1]. RLS is screened for by asking the patient about creeping, tingling, or cramping pain in legs at bedtime, and if the screening is positive, PSG is not routinely indicated. The impact of all sleep disturbances on daily functioning can be determined through clinical interview or by using an outcome of sleep questionnaire (e.g., sleepiness, functioning, and mood).

12.3 Ongoing Research

When screening and assessment are positive for sleep disturbances, there are several interventions to help patients manage chronic and short-term insomnia disorders, OSA, and PLMD/RLS that fluctuate during cancer treatment and survivorship phases [16]. Approaches for managing insomnia include groups of cognitive behavioral, complementary, psychoeducation, exercise, and pharmacologic therapies [17, 18]. Approaches for managing OSA include continuous positive airway pressure and lifestyle modifications such as weight loss [19]. Interventions for PLMD/RLS include pharmacological treatments [20]. The impact of selected approaches needs to be evaluated and modified if the approach is ineffective in improving sleep.

12.3.1 Non-pharmacological Interventions for Insomnia in Patients with Cancer

Which interventions are effective to manage sleep-wake disturbances in people with cancer? AASM has recommended components of cognitive behavioral therapy (CBT) for insomnia as a standard or a guideline for practice in otherwise healthy adults [18]. The National Comprehensive Cancer Network ® (NCCN) presented a new clinical practice guideline for Survivorship in 2013 that includes sleep disorders. The Oncology Nursing Society (ONS) has categorized and synthesized the evidence for sleep-wake disturbances in patients with cancer [21]. No interventions were rated by ONS-Putting Evidence into Practice (ONS-PEP) as "Effectiveness Established," and only cognitive behavioral interventions were rated as "Likely to be Effective." These ratings reflect that the majority of research has been conducted in small samples of cancer patients with sleep-wake disturbances rather than with insomnia, and studies have reported only short-term outcomes. NCCN guidelines and ONS-PEP recommendations complement each other.

Table 12.2 reviews interventions for reducing sleep-wake disturbances/insomnia. These interventions are based on randomized controlled trials among patients in the active treatment and survivorship phases of cancer therapy. Currently, large studies are being conducted to reduce sleep-wake disturbances in patients with cancer, such

Table 12.2 Non-pharmacologic interventions that have been tested for sleep-wake disturbances in patients with cancer

Cognitive behavioral interventions/approach
Instruct patients in the following *stimulus control techniques*:
Go to bed only when sleepy and at about the same time each night
Get out of bed and go to another room whenever unable to fall asleep within 20–30 min, return to bed only when sleepy again
Use the bedroom for sleep and sex only
Instruct patients in the following *sleep-restriction techniques*
Maintain a regular bedtime and rising time each day
Avoid daytime napping; if needed, limit to 1 h or less early to midday; avoid unnecessary time in bed during the day
Instruct patients in the following *relaxation techniques*
Use a relaxation technique within 2 h of going to bed
Schedule a "clear your head time" 90 min before going to bed
Instruct patients in the following *sleep hygiene techniques*:
Avoid caffeine and other stimulants after noon; complete dinner 3 h before bedtime; do not go to bed hungry
Keep the bedroom dark, cool, and quiet. Avoid pets in bedroom
Do not watch television or use computers or tablets in the bedroom
Replace mattress every 10–12 years, pillows more frequently; use light sleepwear and covers
Ensure at least 20 min of daily exposure to bright, natural light soon after awakening
Complementary therapies
Encourage patients to decrease stress by selecting relaxation techniques that suit them, including massage, individual muscle relaxation, mindfulness-based stress reduction, and yoga
Refer patients to practitioners in acupuncture, electroacupressure/acupressure, biofeedback, and/or healing touch therapies
Encourage patients to keep a journal in which they document their deepest thoughts and feelings about their illness and treatment
Encourage patients to decrease stress by focusing on and isolating various muscle groups while moving progressively up and down the body. Encourage focused breathing, with all attention centered on the sensations of breathing, including the rhythm and rise and fall of the chest
Psychoeducation
Provide anticipatory education to patients about sleep hygiene techniques
Provide patients with information regarding specifics of treatment and expected side effects, including sleep-wake disturbances
Repeat this information throughout the treatment
Ensure that the patient's sleep expectations are realistic
Exercise
Rule out bone metastasis or exercise contraindications
Have patient complete moderate exercise (e.g., brisk walking 20–30 min 4 to 5 times per week) at least 3 h before bedtime
Encourage patients to perform strength and resistance training

as yoga during radiation therapy. Other studies are testing behavioral therapy and mindfulness-based stress reduction (MBSR) interventions to reduce several symptoms in patients with cancer, including sleep-wake disturbances. Visit www.ons.org/practice-resources/pep/sleep-wake-disturbance to learn more about the interventions listed on the table and others designed to improve sleep.

12.3.2 Cognitive Behavioral Therapy/Approaches "Likely to Be Effective"

Cognitive behavioral approaches are strategies that include combinations of restructuring and reducing unhelpful thoughts, stimulus control, sleep restriction, relaxation, and sleep hygiene. These approaches are helpful in changing negative thoughts and behaviors surrounding an individual's sleep and function. These approaches seem to be more effective in managing sleep-wake disturbance during the survivorship phase compared to the treatment phase. Patients have reported improved sleep quality, longer sleep duration, shorter time to fall asleep and less time awake during sleep [22–30], and higher sleep efficiency [31].

12.3.3 Complementary Therapies "Effectiveness Not Established"

Complementary therapies include a broad array of techniques designed to diminish stress and promote relaxation. The ONS "Effectiveness Not Established" rating indicates a lack of published evidence from large randomized controlled studies [17] (www.ons.org/practice-resources/pep/sleep-wake-disturbance). Below are some examples:

12.3.3.1 MBSR

MBSR is an intervention that consists of a combination of psychoeducation, meditation, and stress-reducing mental exercises aimed to promote relaxation. One MBSR technique is based on variations of the Kabat-Zinn group approach focusing on psychoeducation, meditation, and yoga [32]. MBSR may involve a tailored component that might affect sleep.

Like cognitive behavioral approaches, MBSR may be more influential for the management of sleep-wake disturbance during the cancer survivorship phase. MBSR has been associated with improvements in self-reported sleep quality in survivors of breast and other cancer diagnoses [32–34].

12.3.3.2 Other Complementary Strategies

Acupuncture and yoga are therapies that have been studied to reduce sleep-wake disturbances in patients with cancer. Acupuncture was associated with less sleep disturbance in patients with malignant tumors during active cancer treatment [35]. Yoga can be performed in a variety of ways, but the general aim is to physically align the body into postures, practice breathing, and mindfulness exercises. Yoga, compared to standard care, was associated with better sleep quality and less reliance on sleeping medications in cancer survivors of mixed diagnoses and various stages [36].

12.3.4 Psychoeducation "Effectiveness Not Established"

The Pan-Canadian Guidelines recommend that all patients receive education about sleep and strategies to manage insomnia [9]. Psychoeducation interventions involve a variety of platforms such as the phone or Internet to impart information to patients. These approaches have been studied with varied success on sleep outcomes in patients with cancer. A web-based education intervention was effective in improving sleep quality in survivors of breast and other cancers [37]. More evidence is needed to determine the effects of psychoeducation interventions on sleep-wake disturbances during cancer treatment and survivorship.

12.3.5 Exercise "Effectiveness Not Established"

Interventions examining the influence of exercise on sleep-wake disturbances in patients with cancer have primarily consisted of strength training and home-based tailored aerobic or walking programs. The evidence is promising for influencing outcomes in patients during active cancer treatment. Subjective sleep quality was improved in patients during treatment for mixed diagnoses of cancer who participated in a variety of physical exercise interventions [38–40] but not in patients with lymphoma. More studies are needed to determine the influence of exercise on sleep-wake disturbances in cancer survivors.

12.3.6 Pharmacological Therapies "Effectiveness Not Established"

12.3.6.1 Insomnia

The effectiveness of the pharmacological management of insomnia has not been established during active treatment or in the survivorship phase of cancer [17]. No large, randomized controlled trials have examined the effect of pharmacological therapies on sleep in patients transitioning through cancer therapies [41].

Pharmacological therapy used for sleep-wake disturbances in otherwise healthy adults includes prescribed medications and supplements. Several medications prescribed for sleep-wake disturbances are classified as psychotropic drugs. These medications have been used off-label for the management of a variety of symptoms of cancer treatment. Psychotropic medications include antidepressants, benzodiazepine and non-benzodiazepine hypnotics, atypical antipsychotics, and anticonvulsants. These medications have sedating/hypnotic effects that are proposed to improve sleep-wake disturbances but need to be used with caution [41].

Antidepressants have varied undesirable side effects associated with their use. Selective serotonin reuptake inhibitors such as paroxetine (Paxil®) have more of a

sedative effect [41]. Paroxetine improved sleep problems in both depressed and nondepressed cancer patients receiving treatment, but the rates of sleep problems remained high [42]. Of major concern, paroxetine was found to inhibit the metabolism and benefit of tamoxifen (Nolvadex®) in women being treated with breast cancer [43].

Medications such as trazodone (Desyrel®) have been used in low doses to improve sleep [41]. A descriptive study reported that trazodone may improve insomnia and nightmares in patients with all types of advanced cancers [44]. However, trazodone should be used cautiously in patients with cardiovascular comorbidities because it may cause orthostasis and lead to falls. Tricyclic antidepressants such as amitriptyline are generally not used due to side effects (i.e., dry mouth) that may be bothersome in patients with cancer [41].

Benzodiazepine sedatives (BDZ) and non-benzodiazepine hypnotics have been used for management of insomnia in patients throughout phases of cancer care. Non-BDZ hypnotics, such as zolpidem (Ambien®) and zopiclone (Lunesta®), are used most often, but evidence of their effectiveness is lacking in patients with cancer [41]. Women with breast cancer or at high risk for developing the disease who had hot flashes accompanied by nighttime awakenings were randomized to double-blinded treatment with zolpidem or placebo that was combined with the antidepressant venlafaxine (Effexor®) XR, 75 mg/day. Women in the zolpidem augmentation group reported improved sleep and quality of life [45]. Benzodiazepine and non-BDZ medications may be effective for short-term insomnia management, but clinicians and patients need to be aware of side effects such as drowsiness that may impair daytime functioning of the cancer survivor.

Antipsychotic medications have been suggested for off-label use to help the nonpsychotic patient whose medical condition contradicts using benzodiazepines. Atypical antipsychotic medications are not approved for use in treating sleep-wake disturbances and are associated with cardiometabolic and anticholinergic effects. Anticonvulsants such as pregabalin influence the same brain chemicals as benzodiazepines and have similar side effects. Metabolism of these medications can be altered due to drug-drug interactions with medications such as corticosteroids, which are commonly given during and after cancer treatment [41]. Herbal supplements such as valerian have not been associated with improved sleep in clinical trials of patients undergoing cancer treatment.

12.3.6.2 OSA

There is currently no recommended pharmacological treatment for OSA [19]. However, the AASM clinical guideline for evaluation and management of OSA in adults recommends positive airway pressure for the treatment of moderate to severe OSA; other appropriate strategies include oral appliances and surgery. Patients with mild OSA may benefit from weight reduction or lying in a side position.

12.3.6.3 PLMD/RLS

The AASM practice parameters recommend standard, guideline, and option levels for the pharmacological treatment of RLS [20]. Dopaminergic medications such as pramipexole (Mirapex®) and ropinirole (Requip®) have a standard level of recommendation. Medication therapies with a guideline level of recommendation include levodopa with dopa decarboxylase inhibitor, opioids, gabapentin (Neurontin®), enacarbil (Horizant®), and cabergoline (Dostinex®). Therapy may include anticonvulsant medications with an option level of recommendation such as carbamazepine (Tegretol®), gabapentin/pregabalin (Lyrica®), and adrenergic medications such as clonidine (Catapres®). Individuals with a diagnosis of RLS due to low iron levels may benefit from iron supplementation.

12.4 Solutions

Cancer survivorship involves many phases in an individual's cancer journey. Along each step of the way, the patient's oncology and/or primary care team needs to be aware of each survivor's residual and late side effects from cancer treatment. Implementing evidence-based interventions into clinical practice is important to both healthcare providers and cancer patients. More emphasis needs to be placed on educating cancer patients to notify their oncology and/or primary care provider team when they experience chronic sleep-wake disturbances with daytime consequences such as fatigue, emotional distress, and lower physical functioning. Solutions need to be readily available for patients who complain of non-restorative sleep, and survivorship care plans need to address this issue.

However, patients who seek resources to manage sleep-wake disturbances often find that the process currently occurs at an individual, rather than a system, level. Patients may locate reliable resources at websites on the World Wide Web, such as those listed on Table 12.3. As evidence matures, guidelines will be established and disseminated in more clinics.

Table 12.3 Online resources to manage sleep-wake disturbances

National Cancer Institute (NCI) PDQ®	http://www.cancer.gov/cancertopics/pdq/supportivecare/sleepdisorders/HealthProfessional
National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology: Survivorship	http://nccn.org/professional http://nccn.org/patients/default.aspx
National Sleep Foundation	http://www.sleepfoundation.org/article/how-sleep-works/how-much-sleep-do-we-really-need
Oncology Nursing Society Putting Evidence Into Practice (ONS-PEP)	https://www.ons.org/practice-resources/pep/sleep-wake-disturbances

Two strategic solutions are not currently available in most oncology and primary care settings. One strategy is to use evidenced-based protocols to screen and assess for sleep-wake disturbances in adults with cancer [46]. Protocols are an inexpensive clinical resource to provide efficient and effective screening and provide a framework for appropriate clinical symptom assessment, treatment, and follow-up. A second strategy is for healthcare professionals to use the electronic medical record (EMR) to track screening methods, such as tools used and outcomes. In the future, health professionals will use the EMR at the system level to track screening, assessments, treatments, and outcomes [47].

The next section will discuss solutions that are ready to be tested in clinical oncology and/or primary care settings to improve screening, assessment, and treatment of sleep-wake disturbances in cancer patients in all phases of the cancer trajectory.

12.4.1 Screening

Regular screening for sleep-wake disturbances needs to begin at the time of diagnosis and progress during treatments and at regular intervals during the survivorship phase. Clinicians need to screen patients for pain and other distressing symptoms, such as disturbed sleep, at each encounter with the healthcare team. The tools used to screen patients need to have established reliability and validity in detecting and predicting sleep-wake disturbances in similar patient populations. Recommended tools are listed previously in this chapter.

12.4.2 Assessment

Primary care providers and oncology clinicians need education and training to perform sleep assessments. The assessment needs to include questions regarding co-occurring symptoms of anxiety, depression, and fatigue; history of comorbid conditions; and the use of prescribed and over-the-counter medications. Sleep disturbance assessment questions need to include sleep time, sleep latency, daytime napping, sleepiness during the day, sleep quality [9], shift work, typical bed time, and typical wake time. The frequency and quantity of use of nicotine and alcohol should be assessed [48]. The use of actigraphy and sleep diaries to collect 1–2 weeks of data may be helpful in assessing an individual's typical sleep patterns. Questions regarding social functioning, sexual relationships, employment, and beliefs about sleep are helpful when assessing the individual's level of disability, as well as perceptions of sleep [9]. An accurate diagnosis of the sleep disturbance/disorder may require a referral to a sleep specialist for PSG or other diagnostic tests to make a diagnosis and prescribe an appropriate treatment.

12.4.3 Treatment

The treatment of sleep-wake disturbances in patients with cancer needs to take into account all factors that could cause short-term and chronic sleep disruption (e.g., pain, anxiety, depression, cancer disease process, and comorbid diseases). More than one sleep disorder can occur in cancer patients (e.g., insomnia and OSA). In order to prevent or reduce adverse health outcomes such as cardiovascular events and lower quality of life, the factors causing sleep deprivation and sleep disruption need to be diagnosed and treated.

Cognitive behavioral therapy (CBT) approaches have been shown to be "likely to be effective" in treating insomnia in cancer patients (ONS-PEP), and the stepped-care approach is a viable, yet undeveloped solution to treating both short-term and chronic insomnia [49, 50]. Figure 12.1 illustrates the stepped-care approach that uses online self-directed cognitive behavioral therapies (CBT) as first-line treatment of insomnia. Short-term pharmacological interventions may be necessary until CBT interventions have been delivered long enough to become effective, which can take up to 6 weeks [9]. An individualized stepped-care CBT approach is recommended with more severe cases of insomnia requiring more intense interventions [49, 50].

All patients who report insomnia should receive education about sleep hygiene techniques. The clinician can educate the patient to use sleep hygiene techniques on a daily basis and should discuss the patient's sleep expectations. An interactive approach can be used during the teaching session, including educational pamphlets and other electronic resources. Providing information to the patient allows them to revisit the information after the teaching session.

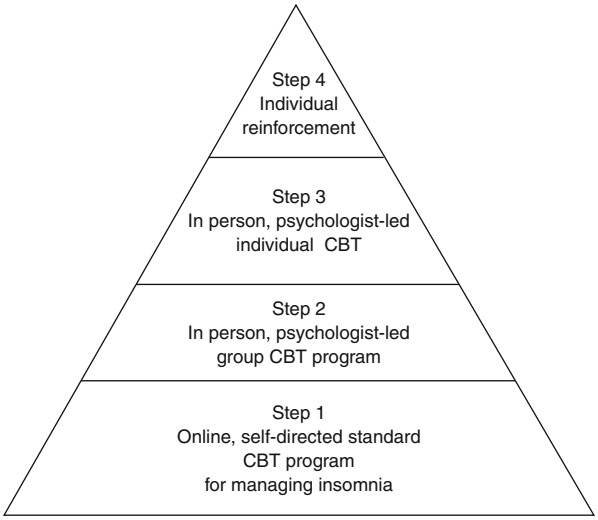

Fig. 12.1 Example of stepped-care model. Note: *CBT* cognitive behavioral therapy

The first step in the CBT-insomnia treatment plan is recommended for patients who had implemented the sleep hygiene interventions at home but still experienced insomnia. The interventions that are used in this type of CBT include an online, self-directed standard CBT for insomnia program with the use of books or the Internet to provide therapies. The patient also may take part in a more manual approach to treatment, which includes direct interaction with providers trained in CBT. Therapies may be provided in a group meeting setting [49, 50].

The second step of the CBT model is implemented when the patient's insomnia symptoms do not show improvement after the self-directed program. The patient is referred to a psychologist or a trained nurse-led group CBT intervention. The CBT sessions can take place in a person-to-person format or can occur online. For patients with cancer, the guidelines recommend that those who are need of more intense CBT undergo multiple meetings with the specialist. The third step of the CBT model is in-person, psychologist-led individual CBT. Individual reinforcement of CBT is an option for some patients [50]. While the patient is undergoing CBT, clinicians need to advise their patients to also take part in activities that may improve sleep, such as exercise [9].

If the CBT stepped-care approach to the treatment of insomnia is not effective after 8 weeks, the use of pharmacologic interventions may be necessary after the risk-to-benefit ratio has been discussed with the patient. A short-term use of medication may be in order, taking drug-drug interactions into account. If the patient is too ill or unable to complete CBT, it is reasonable to keep the patient on medication long term [9].

12.5 Future Directions

AASM is making the systematic integration of sleep disorder screening in the EMR a healthcare priority. Routine screening will increase the efficiency of diagnosing sleep disorders. The electronic documentation of sleep disturbance screening, followed by assessment, will assist oncology and primary care clinicians to use a streamlined system to enhance the referral process [1]. The process will start when a cancer patient arrives for an initial consultation. The primary care provider will access a sleep-wake disturbance protocol that will indicate when it is appropriate to screen patients for sleep-wake disturbances [48]. Valid and reliable sleep disturbance screening tools will be available for use by the clinician. A trained clinician will conduct an assessment if a screening tool indicates the need. If the provider's assessment and evaluation indicate the patient may be experiencing insomnia, OSA, RLS/PLMD, or any other type of sleep disorder, a referral will be made to a sleep specialist for further evaluation using PSG and other diagnostic tests. Selection of an appropriate online or in-person treatment will be individualized, with consideration given for patient preference. Treatment of sleep disorders will improve quality of life and reduce negative health outcomes for cancer survivors.

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Nutrition and the Cancer Survivor

13

Mary Marian and Dianne Piepenburg

13.1 The Problem

Approximately 1.6 million new cases of cancer are diagnosed annually, accounting for 22.9 % of deaths in the USA [1]. When deaths are aggregated by age, cancer has surpassed heart disease as the leading cause of death for individuals under the age of 85 years. For men, prostate cancer is the most commonly diagnosed cancer followed by lung and colorectal, while breast, lung, and colorectal cancers are the most commonly diagnosed cancers in women. These four cancers account for one-half of the total cancer deaths. Additionally in the USA, approximately 600,000 adults are expected to die annually from cancer, accounting for a little over 1500 deaths per day.

According to the American Institute for Cancer Research (AICR), following the AICR and World Cancer Research Fund (WCRF) recommendations for nutrition, physical activity and lifestyle could prevent one-third of the most common cancers that afflict adults in the USA [2]. During their systematic review, the authors concluded that estimates for prevention related to particular dietary aspects, daily physical activity, and maintaining a healthy weight related to some types of cancer were significantly affected [3, 4].

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13.2 Evidence

In 2007, the American Institute for Cancer Research (AICR) together with the World Cancer Research Fund (WCRF) published lifestyle recommendations for reducing cancer risk in adults [4]. These recommendations were based on an extensive meta-analysis and systematic review of over 500 studies. The AICR has continued to systematically review the literature on an annual basis to provide update-to-date recommendations for breast, pancreatic, ovarian, endometrial, and colorectal cancer (Table 13.1).

Recent research has shown that adherence to the AICR/WCRF guidelines is associated with a reduction in mortality not only from cancer but also other comorbidities [6–8]. To highlight this, Arab et al. found that a higher adherence score to the guidelines was inversely associated with the development of highly aggressive prostate cancer (OR = 1.38; 95 % CI, 1.10–1.74). Similarly, the VITamins and Lifestyle (VITAL) study also found that adherence to the AICR/WCRF recommendations was associated with a lower cancer-specific mortality rate. For study participants meeting at least five of the recommendations, cancer-specific mortality was reduced by 61 %. There was no difference in association based on gender or age (HR, 95 % CI, 0.76–0.92), but appeared stronger in nonsmokers. These findings are further supported by the results of the European Prospective Investigation into Nutrition and Cancer (EPIC) cohort study which also found that a greater adherence to the AICR/WCRF lifestyle recommendations for diet, physical activity, and body weight had a 34 % lower hazard of death when compared to poor adherence after 12 years of follow-up [6]. Lastly, the results of the Cancer Prevention Study II cohort study and Women's Health Initiative found that adherence to cancer prevention guidelines for lifestyle published by the American Cancer Society (ACS) resulted in a 30 % lower cancer-specific mortality rate for men and a 24 % reduced rate for women [9].

This chapter will provide a review of the current evidence regarding nutrition and lifestyle recommendations for the cancer survivor. An individual is considered a cancer survivor at the time of diagnosis through the continuum of treatment, monitoring, recovery, and/or living with advanced cancer and end of life [1]. This chapter

Table 13.1 Summary of American Institute for Cancer Research and World Cancer Research Fund lifestyle recommendations [11]

Maintain a healthy body weight
>5 servings vegetables/fruit daily
Select low-fat foods
Select high-fiber foods
Reduce intake of simple sugars/refined CHO/fructose
Limit red meat (18 oz./week); avoid processed/charcoaled/well-done meat or smoked meats
>Risk for colon, esophageal, lung, pancreatic, and endometrial cancers
Moderation in alcohol consumption
>Risk for mouth, esophageal, colon, liver, and breast cancers
Maintain a physically active lifestyle

will also review the current recommendations on diet, physical activity, and body weight management in regard to cancer recurrence prevention, treatment recovery, and improvement on persistent treatment-related side effects such as weight gain and fatigue.

13.3 Solutions

13.3.1 Manage Body Weight

Energy balance is integral to reducing the risk of developing many chronic diseases associated with excess body weight, including cancer [10]. Energy intake and daily physical activity are key factors in the regulation of body weight. While there may be some limitations for using BMI as an indicator of "healthy" body weight for adults, the range of 18.4–24.9 kg/m^2 has been accepted by the healthcare community as a healthy body weight range to reduce risks of comorbidities.

Prior to the development of cancer screening and detection guidelines, many cancer patients were diagnosed with disease in advanced stages [11]. Antineoplastic treatment(s) and the disease itself frequently resulted in inadequate oral intake due to the presence of nutrition impact symptoms such as anorexia, nausea, and early satiety [11]. As a result, involuntary weight loss, malnutrition, and cachexia were common outcomes [11]. Fortunately, advanced technologies and techniques today have helped improve the detection and diagnosis of cancer when it is in the early stages – the stages when it is most treatable and curable.

Currently, there is a global obesity epidemic, and cancer survivors today are more likely to be overweight or obese at the time of their diagnosis [11]. The National Cancer Institute estimates that about 500,000 new cases of cancer will be diagnosed in the USA by 2030 if the current obesity epidemic continues [12]. With this, evidence is emerging that being overweight or obese at the time of diagnosis of certain cancers, such as prostate, endometrial, pancreatic, and esophageal, is associated with adverse outcomes including increased risk of disease recurrence and reduced survival [3].

Traditionally, many cancer survivors experienced unintentional weight loss as a consequence of antineoplastic treatment. Today, many treatment regimens are associated with weight gain. Therefore, survivors who are overweight or obese should be counseled to avoid weight gain during cancer treatment [3, 4]. Furthermore, intentional weight loss posttreatment for cancer survivors who are overweight or obese may reduce not only risk of recurrence but also risk of other health-related conditions such as cardiovascular disease, diabetes, and hypertension.

13.3.2 Limit Red Meat Consumption and Avoid Processed Meats

Red meat (e.g., beef, pork, lamb) is often defined as the flesh from animals that are higher in red muscle fibers than white muscle fibers (e.g., fish and chicken). While

there is no standardized definition for processed meats, it is generally accepted that meats preserved through curing, salting, smoking, or the addition of preservatives such as sodium nitrite are usually considered processed [13]. Common processed meats include bacon, lunchmeats such as ham, pastrami, and turkey, as well as sausage. Consumption of red meat reportedly continues to increase both in the USA as well as globally [13].

The 2007 expert report published by the WCRF and AICR recommended limiting the intake of red meat to 18 ounces per week, while processed, charcoaled, well-done, and smoked meats should be avoided altogether [4]. This report also concluded that the consumption of red and processed meats was convincingly associated with the development of colorectal cancer based on the evidence from 16 cohort studies and 71 case-control studies [1]. Furthermore, the 2011 WCRF/AICR continuous update project regarding colorectal cancer further supported the 2007 recommendation [4, 14]. The same report also found evidence to suggest that consumption of red and processed meats may increase the risk for endometrial, esophageal, lung, stomach, pancreas, and prostate cancers; however, the panel determined that the evidence was limited and, in some cases, conflicting. Consistent with the WCRF/AICR expert report, the National Institutes of Health (NIH) and American Association of Retired Persons (AARP) published a study that noted the positive association between red meat/processed meat intake and colorectal cancer [15]. Additionally, a meta-analysis published by Alexander et al. that included 28 prospective studies also found a significant association between colorectal cancer and processed meat intake (high compared with low intake, 1.16; 95 % CI, 1.10, 1.23) [16]. However, it was concluded overall that given the weak magnitude of the evidence and lack of standard definition describing what constitutes "processed meat," the current data based on epidemiologic studies may not be sufficient.

While the precise etiology of why consumption of red and processed meats increases the risk for cancer is unclear, a mechanistic role has been proposed for the production of heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH), and N-nitroso compounds and the presence of heme iron [13]. How meat is cooked appears to be the tipping point, since meat cooked to well done over high temperatures results in the formation and deposition of PAHs in the meat. Additionally, HCAs are produced when the amino acids, creatine, and sugars found in the muscle tissue of meat react at high temperatures. Based on animal studies, these compounds are considered carcinogens. The presence of iron within the myoglobin of the meat also increases nitrosamine formation when cooked, causing damage to DNA. In addition, the nitrates/nitrites and salt used to process meat contribute to nitrosamine production and also act as carcinogens in animals [15].

While research has shown an association between the consumption of red and processed meat and colorectal cancer, information remains somewhat inconclusive in respect to red meat and processed meat consumption with other cancer diagnoses [3]. However, evidence indicates that the risks of consumption outweigh the benefits in respect to other cancers, as well as all-cause mortality. To confirm this statement, Pan et al. performed a prospective, observational study of 37,698 men and 83,644 women and found that a 1-serving per day increase in red meat consumption was associated with an increase in total mortality and cancer mortality [17]. In a

meta-analysis performed by Larsson, Orsini, and Wolk, an increased consumption of 30 g/day of processed meat was associated with a statistically significant 15 % increased risk of stomach cancer [18]. An increased 16 % risk of lung cancer was also evident within a cohort of approximately 500,000 individuals with the highest intake levels of red meat and processed meat [19]. Because the body of evidence currently available reflects a potential association between red and processed meat consumption, the WCRF/AICR guidelines recommend that individuals who consume red meat limit their intake to no more than 18 ounces/week and consume very little – if any – processed meats [4, 14].

13.3.3 Maintain a Physically Active Lifestyle

Regular, physical activity is associated with a multitude of benefits for all children and adults and, as such, is widely recommended by health organizations worldwide. Physical activity is associated with reducing the risk for the most common chronic diseases including cardiovascular disease, type II diabetes, and hypertension with evidence accumulating that risk for some types of cancers can also be reduced [3]. The results from prospective observational studies reflect that regular physical activity also can be beneficial for cancer survivors during and posttreatment for improving aerobic fitness, endurance, and quality of life while reducing fatigue, depression, and insomnia. Moreover, a lower risk of mortality associated with higher levels of moderate-to-vigorous physical activity has been reported for breast, prostate, and colorectal cancer survivors [3]. To highlight this, a meta-analysis and systematic review published by Schmid and Leitzmann concluded that in comparison to breast and colorectal cancer survivors who make no changes in their physical activity levels from pre- to post-diagnosis, survivors who increase their physical activity levels by any amount experience a reduction in total mortality risk (RR = 0.61; 95 % CI = 0.46–0.80) [20].

Current recommendations for regular physical activity encourage all Americans to obtain 150 min weekly of moderate physical activity or 75 min of vigorous activity [3]. With respect to breast and colorectal cancer survivors, Schmid and Leitzmann found a decrease of 24 % in total mortality and a 28 % reduction, respectively, in those who exercised at least 150 min/week at a moderate intensity [19]. Hardee et al. similarly reported that resistance exercise was associated with a 33 % decreased risk for all-cause mortality in cancer survivors (95 % CI, 0.45–0.99) [1]. Although the precise mechanisms involved have not been clearly elucidated, the benefits are thought to be associated with reduced levels of circulating insulin and proinflammatory mediators as well as alterations in inflammatory pathways [20, 21].

13.3.4 Exercise During Cancer Treatment

Exercising during and after treatment appears safe and is associated with benefits such as improved physical functioning, exercise tolerance, body composition, cardiopulmonary fitness, and muscular strength, in addition to less fatigue, depression,

and anxiety – factors that influence quality of life [3]. Weight resistance training during treatment has also been found to preserve lean body mass while decreasing the risk for gaining adipose tissue.

Despite the many benefits associated with physical activity, many cancer survivors remain sedentary [3]. A number of barriers may preclude survivors from obtaining regular physical activity, including: stage of disease, type of treatment undergoing or completed, and current health status. However, survivors who report regular physical activity patterns prior to diagnosis are more likely to continue exercising during and posttreatment. While beginning an exercise program during treatment may be difficult for some individuals, any exercise should be encouraged to obtain the reported benefits. Research shows that many cancer patients are willing to exercise through treatment, including the elderly. In fact, in a study by Sprod et al. on 408 elderly cancer patients (mean age of 73 and age range from 65 to 92), 46 % of the patients (65 years and older) reported exercising during treatment, as well as less shortness of breath and fatigue with improvements in overall general health and well-being during and after treatment [22].

13.3.4.1 Physical Activity and Clinical Outcomes

Much of the current available data regarding physical activity posttreatment clinical outcomes is derived from breast cancer survivors, with the body of the evidence reflecting an inverse association between self-reported regular physical activity and cancer-specific mortality as well as all-cause mortality [3]. Risk reduction ranges for cancer-specific and all-cause mortality are 15–67 % and 18–67 %, respectively. However, about 180 min per week of exercise of moderate intensity to ≥500 min/week of moderate intensity activity may be required to obtain those benefits [20]. It is important to remember that the type of activity should be tailored based on the survivors' treatment history, current clinical status, and ability to exercise.

Currently, the association between physical activity and risk reduction for all cancers is not known. For example, an inverse relationship between regular physical activity and colon cancer risk was found in a recent meta-analysis [24]. In addition, an association has also been found between exercise and rectal cancer [23]. On the other hand, regular, physical activity prior to a diagnosis of stage II and III colorectal cancer has been linked with longer disease-free survival, increased levels of insulin-like growth factor binding protein-3, and a significant decrease in disease-specific death [21, 25]. Study investigators theorize that increased binding protein levels may positively modulate the insulin-IGF-1 axis.

ACS guidelines on nutrition and physical activity recommend that cancer survivors in all phases of the cancer care spectrum (e.g., treatment, recovery, and life after recovery) be as physically active as possible [3]. The ACS expert panel reiterated the recommendations provided previously by the American College of Sports Medicine [3, 26]:

1. Adults 18–64 years old should obtain 150 min of physical activity weekly of moderate intensity, or 75 min weekly of vigorous activity, or a combination of the two

Table 13.2 Summary of the American College of Sports Medicine recommendations for physical activity for cancer survivors [11]

Type of activity	Goals
Adults aged 18–64 years:	
Moderate intensity	150 min/week
Vigorous intensity	75 min/week
Or combination of above	
Weight resistance training utilizing all muscle groups	Twice weekly
Guidelines also recommend patients be evaluated for the presence of peripheral neuropathies and musculoskeletal and/or fracture risk based on disease and treatment history. Morbidly obese individuals could require an additional medical assessment	

2. Strength training should be included in any exercise regimen with weight-resistance activities that utilize all muscle groups at least twice weekly (Table 13.2).

Research also reflects a favorable association between post-diagnosis physical activity level and the risk for recurrence, cancer-related deaths, as well as overall mortality for breast, colorectal, ovarian, and prostate cancer survivors; higher activity levels are associated with a risk reduction for recurrence and mortality. The risk for developing other chronic diseases, such as cardiovascular disease, type II diabetes, and hypertension, which also affect cancer survivors, is also reduced with regular physical activity.

In summary, data regarding physical activity for cancer-related risk reduction and improved survival is promising; however, these observations require confirmation with prospective randomized trials. Indeed, a number of clinical trials are now underway to further investigate these findings and address our current gaps in knowledge.

13.3.5 Consume a Healthy Diet, with an Emphasis on Plant-Based Foods

Observational studies have indicated that one's diet may affect cancer progression, risk of recurrence, and overall survival [3]. In addition, cancer survivors are at high risk for other chronic diseases including diabetes and heart disease. Therefore, dietary recommendations include adhering to the principles of a general, healthful diet put forth by the ACS and AICR, which includes adequate intake of macronutrients through consumption of fruits, vegetables, whole grains, and lean proteins [4, 27].

The foundation of a diet consists of carbohydrate, protein, and fat – all of which contribute energy (i.e., calories) within the diet. Overconsumption of these components not only can lead to increased risk of heart disease and diabetes but also to overweight and obesity. Overweight and obesity have also been shown to increase the risk of multiple comorbidities, including cancer [3]. Therefore, the goals of cancer survivors should include consumption of energy that is consistent with one's energy usage. While various organizations have their own recommendations

for diet composition for the adult, general intake recommendations are carbohydrate (45–65 % of calories), protein (10–35 % of calories), and fat (10–35 % of calories) [28].

Cancer can also cause a milieu of metabolic and physiologic effects that in turn can significantly alter the need for protein, carbohydrate, fat, vitamins, and minerals [3]. The ability to ingest adequate nutrition may be also be adversely affected due to disease and/or treatment-related side effects including anorexia, taste alterations, gastrointestinal changes, and other cancer and cancer treatment-related side effects. These, in turn, may lead to significant weight loss and poor nutritional status; therefore, during these instances, the goal is to prevent or reverse nutrient deficiencies and preserve lean body mass by treating and minimizing nutrition-related side effects. By identifying and treating nutrition-related impact symptoms, functional status and quality of life can also be improved (Table 13.3) [3].

The primary factor that has been shown to potentially influence one's risk of cancer is overconsumption of energy. Obesity is due to the higher body adiposity that typically ensues when this occurs. This increased adiposity results in increased risk of ill effects on one's health including production of reactive oxygen species, hyperinsulinemia, increased IGF-1 production, and increased estrogen production [29].

Breast cancer patients have been the primary focus of research on determining how diet and food choices affect progression and negative survival outcomes. More recently, however, there has been an increased focus on those afflicted with colorectal and prostate cancer and the effect that diet has on progression, recurrence risks, and survival.

Two large-scale, randomized controlled trials – the Women's Intervention Nutrition Study (WINS) and the Women's Healthy Eating and Living study (WHEL) – studied whether a diet lower in fat following the diagnosis of early-stage breast cancer can improve cancer outcomes [30]. The WINS study showed an inverse relationship between a low-fat diet (less than 15 % of calories from fat) and relapse-free survival with a 24 % decline in new breast cancer events [5]. Interestingly, an increased benefit was seen in only those women diagnosed with estrogen receptor-negative (ER-) disease. Conversely, the WHEL study did not find a statistically significant improvement in relapse-free survival despite a diet rich in vegetables, fruit, and fiber and, subsequently, lower in fat (aiming for 15–20 % of energy intake from fat). However, it was also found that women in this study failed to achieve these goals. It is important to note that women enrolled in the WINS study also experienced an average weight loss of 6 lb while those enrolled in the

Table 13.3 Benefits and barriers to exercise [11]

Benefits	Barriers
Reduced fatigue	Chemotherapy
Improved physical functioning	Fatigue
Improved mood and less depression	Tender wounds
Increased coping skills	Age
Improved quality of life	Economic status
Lean body mass	
Long-term health benefits	

WHEL study did not lose a statistically significant amount of weight (less than 1 kg difference between control and intervention group); therefore, it is not known if the results of the WINS study were due to the weight lost or diet modification.

Research has shown that a diet high in animal-based foods is associated with an increased risk of prostate cancer [31]. In 1993, Giovannucci et al. analyzed the data in the Health Professionals Follow-Up Study and found that total fat consumption was directly related to risk of advanced prostate cancer (age- and energy-adjusted RR = 1.79, 95 % CI = 1.04–3.07; *P* [trend] = 0.06) [32]. More recently, Aronson et al. found that men with a diagnosis of prostate cancer who adhered to a low-fat (15 % of total calories), high-fiber, soy protein-supplemented diet experienced a significant decrease in growth of prostate cancer cells compared to those who incorporated a Western-type diet (40 % calories from fat) ($P = 0.03$) [33].

In respect to the colorectal cancer population, the data thus far has been limited in identifying the benefits of dietary interventions and cancer survival outcomes [3]. In a large, prospective, observational study of those with stage III colon cancer, Meyerhardt et al. tried to determine if dietary choices modify colorectal cancer outcomes [34]. Results indicated that a diet high in fruits and vegetables, poultry, and fish was not associated with cancer recurrence or mortality. However, a significant decrease in disease-free survival was seen in those consuming a Western type of diet, which is rich in animal proteins, saturated fat, and processed food items (AHR 3.25, 95 % confidence interval [CI] 2.04–5.19; *P* for trend <0.001) [34].

Americans currently consume foods that contain large amounts of sodium, added fats, added sugars, and refined grains – all of which can lead to overweight/obesity and chronic disease [28]. As discussed above, this Western-type diet has been associated with decreased cancer survival and increased risk of all-cause mortality [3]. Conversely, higher intakes of vegetables and fruits have been linked to a lower incidence of chronic disease and cancer, including those of the colorectum, stomach, lung, oral cavity, and esophagus [35]. Vegetables and fruits are also lower in caloric density and higher in fiber and water – all of which may lead to decreased energy intake and assist in maintaining, or obtaining, a healthy weight [27].

Numerous studies have tried to identify specific dietary components (i.e., vitamins, minerals, phytochemicals) within these foods that may provide cancer-protective qualities, but research thus far has not shown significant benefit [28]. However, research has shown the benefit in the consumption of a wide variety of fruits and vegetables, thus supporting the notion that the synergistic effects of the vitamins, minerals, fiber, and phytochemicals, in addition to their low caloric density, provide health benefits. Presently, the American Cancer Society (ACS) recommends an intake of vegetables and fruits of at least two and one-half cups, or five servings per day, to reduce one's risk of cancer [27].

When cancer treatments profoundly alter oral intake, the focus of the primary nutrition goal may change to optimize intake by encouraging the cancer survivor to eat or drink "whatever" they can in order to meet their individualized nutritional needs as best as possible [27]. Current research confirms the benefit of enlisting the services of an oncology nutrition expert to provide individualized nutrition education and support to maximize the patient's nutritional status.

13.3.6 Limit Intake of Foods and Drinks That Promote Weight Gain

According to the American Institute for Cancer Research, one-third of Americans are overweight and one-third are considered obese [5]. While inactivity is a significant contributing factor to this epidemic, a Western-type diet, which is high in refined grains and sugars and low in nutrient density, also plays a major role [4]. It has also been theorized that consuming a diet high in sugar increases cancer risk or progression [3]. This is not true. However, consumption of food items high in sugar (i.e., honey, raw sugar, brown sugar, high-fructose corn syrup) can add a significant amount of calories. This may lead to overconsumption of energy, thus adding a substantial amount of unnecessary energy to the diet, potentially leading to weight gain. In addition, these items are also typically not rich in nutrients and could replace items that are rich in vitamins, minerals, and fiber and are less calorically dense. In addition, refined grains are those in which the whole grain has been stripped of its bran and germ. This results in loss of fiber, such as lignans, vitamins, minerals, and phytochemicals – all of which have been linked to decreased risk of cancer. Even though refined grains may be enriched, or have had some vitamins and minerals added back in, this is not enough to make it a complete replacement for its whole-grain counterpart.

Current recommendations encourage limited consumption of foods and drinks that promote weight gain and choosing whole-grain foods instead of refined-grain products including pastries, candy, sugar-sweetened breakfast cereals, and other high-sugar foods [4, 27]. When working with cancer survivors, clinicians should take a patient-centered approach that utilizes evidence-based information that encourages a plant-based diet rich in fruits, vegetables, and whole grains and limited in refined sugar and processed grains (Table 13.4).

13.3.7 Limit or Omit Alcohol

> The evidence that all types of alcoholic drinks increase the risk of a number of cancers is strong. There is convincing evidence that alcohol increases the risk of cancer of the mouth, pharynx, larynx, esophagus, colorectum, liver, and breast. [4]

Table 13.4 Resources for clinicians and cancer survivors

The American Institute for Cancer Research	www.aicr.org
The American Cancer Society	www.cancer.org
The National Cancer Institute	www.cancer.gov
Oncology Nutrition Dietetic Practice Group	www.oncologynutrition.org
National Center for Complementary and Alternative Medicine	www.nccam.nih.gov
The Academy of Nutrition and Dietetics	www.eatright.org

Alcohol modifies one's risk for cancer via numerous processes, one of which includes the known effect alcohol has on increasing circulating levels of estrogens [36, 37]. In addition, alcohol's primary metabolite is acetaldehyde, a contributor to oxidative stress and inflammation. Acetaldehyde is also a highly reactive and toxic by-product that may contribute to tissue damage by the formation of damaging molecules known as reactive oxygen species (ROS) and induce a change in the reduction–oxidation (or redox) state of liver cells. These processes may lead to inflammation within the liver and affect the clearance of chemotherapeutic drugs, thus worsening toxicities [3].

Alcohol has been shown to increase the risk of mortality of a variety of cancers [38]. In respect to breast cancer, epidemiologic evidence suggests a positive relationship between moderate alcohol intake and increased risk of breast cancer. The Life After Cancer Epidemiology (LACE) Study followed women with early-stage breast cancer for 2 years. Results indicated that women with a diagnosis of early-stage breast cancer who consumed three to four standard drinks or more per week were associated with a 1.3- and 1.5-fold increased risk of breast cancer recurrence and death [39]. These results were confined to postmenopausal women and those who were overweight or obese.

Findings have been similar in those diagnosed with head and neck, liver, esophageal, and colorectal cancer. Park et al. assessed the impact of pre-diagnosis alcohol consumption on cancer survival in male cancer patients [40]. Results indicated that when compared with nondrinkers of alcohol, heavy drinkers (124.2 g alcohol/day) had increased death rates for head and neck (HR, 1.85; 95 % CI, 1.23–2.79) and liver cancers (HR, 1.25; 95 % CI, 1.11–1.41). Lower survival rates in those with esophageal cancer were also associated with increased alcohol consumption ($P < .001$ for trend). A meta-analysis performed by Fredriko et al. also indicated that increased alcohol consumption increases the risk of colorectal cancer [41]. Compared to nondrinkers/occasional drinkers of alcohol, moderate drinkers (>1–4 drinks/day or 12.6–49.9 g/day) had a 21 % increased risk, while heavy alcohol consumers (≥4 drinks/day or ≥50 g/day ethanol) had a 52 % increased risk for colorectal cancer. Dose–risk analysis also indicated a statistically significant 7 % increased risk for colorectal cancer with light alcohol consumption (10 g/day).

Because alcohol consumption has been shown to increase one's risk for cancer and cancer recurrence and worsen outcomes when one already has a cancer diagnosis, it is crucial that healthcare providers educate their patients on the health effects of alcohol consumption. This includes encouraging individuals to limit, or omit, alcohol from their dietary routine. If consumed at all, people who drink should limit their intake to no more than two drinks per day for men and one drink per day for women. A drink is defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80-proof distilled spirits [27].

13.3.8 Do Not Use Supplements for Cancer Preventive Purposes

Since the latter half of the twentieth century, Americans have been increasingly interested in the use of supplements as a natural alternative to traditional medicines [42]. Because these products are considered "natural," they are often viewed as

being safer than prescription medications. However, approximately 40 % of pharmaceutical products are derived from plants, with at least 30 plant-derived compounds currently being investigated for cancer therapies. Because the supplement industry is responsible for ensuring its own safety, the over-the-counter availability and self-dosing of supplements may also pose a risk to one's health. In addition, at present, there is not sufficient evidence to show that dietary supplements reduce cancer risk, but there is evidence that does show high-dose supplements may potentially increase cancer risk [27].

Supplement use in those who have been diagnosed with cancer, or who are long-term survivors, has also increased in recent years [42]. In 2003 and 2006, it is estimated that 64 % and 81 % of individuals, respectively, used supplements. Much of the interest in supplement use within the oncology setting arose after preliminary research indicated that specific vitamins and minerals may improve outcomes for breast, colorectal, lung, and prostate cancer.

Among multiple studies looking at the incidence of cancer in women who used calcium and vitamin D supplements, two notable reports include the Nebraska Trial and the Women's Health Initiative (WHI) [43, 44]. The Nebraska Trial aimed to determine if calcium alone or calcium with vitamin D reduced the incidence of all types of cancer. This 4-year double-blind, randomized placebo-controlled trial of 1179 postmenopausal women randomized participants to receive 1400–1500 mg supplemental calcium/day, supplemental calcium plus 1100 IU vitamin D3/day, or placebo. Results showed a positive association between supplemental calcium and vitamin D use and reduced risk of all-cancer risk ($P < 0.03$). In respect to breast cancer risk, the WHI was a large trial that initially sought to determine if 1000 mg elemental calcium with 400 IU vitamin D3 would reduce the incidence of hip fracture, with invasive breast cancer being a secondary outcome. Between the placebo and supplement groups, cancer incidence was similar, with no effect of supplementation on reducing breast cancer risk being shown. It is also important to note that women in this study were also taking their own calcium supplements, which may have influenced the noted outcome.

In respect to colorectal cancer and supplements potentially decreasing risk, the Nurse's Health Study had 89,448 women complete a semiquantitative food-frequency questionnaire at baseline, with updates being performed two subsequent times thereafter [45]. Results indicated that while there was not a substantial inverse association between calcium intake and colorectal cancer, there was a small, inverse relationship between dietary vitamin D intake and colorectal cancer.

Vitamin E, selenium, vitamin C, and beta-carotene have also been studied in efforts to discern if use of these supplements would reduce a man's risk of prostate cancer. This included the large randomized placebo-controlled trial: Selenium and Vitamin E Cancer Prevention Trial (SELECT) [46]. In this study, participants were provided with a placebo, 400 IU vitamin E, 200 mcg selenium, or both for

7–12 years. Results indicated no statistically significant differences in the diagnoses of prostate cancer between any of the four groups.

Within the α-Tocopherol, β-Carotene Cancer Prevention (ATBC) trial, results with respect to reducing lung cancer risk were also not positive [47]. In participants who received 20 mg daily of beta-carotene, evidence of increased incidences of lung cancer was found, while supplementation of vitamin E saw neither a positive or negative effect. It is also important to note that the increased incidence in the beta-carotene group was seen in those who were heavier smokers and had a higher alcohol intake. Similarly, the Beta-Carotene and Retinol Efficacy Trial (CARET) had negative outcomes with beta-carotene (30 mg/day) and vitamin E (25,000 IU/day) supplementation. In fact, this study was halted due to the increased incidence of and total mortality from lung cancer.

Current recommendations encourage individuals to not use supplements for cancer prevention. As noted, a significant number of those diagnosed with cancer use dietary supplements, some of which may be safe or unsafe [42]. Healthcare professionals should encourage open dialogue between themselves and patients in order to develop a patient-centered nutrition care plan and also to make the cancer survivor feel empowered to make decisions. Registered dietitians nutritionists (RDN) are also helpful in discussing various conventional and functional foods that may also meet the cancer survivors' goals and wishes (Table 13.5).

13.4 Future Directions

Cancer survivors look to clinicians for advice on how to prevent recurrence and how to address persistent treatment-related side effects such as weight gain, peripheral neuropathy, and fatigue. Patient-centered care is the foundation for lifestyle counseling and implementation of lifestyle recommendations. Challenges with oral intake, body weight, ability to ambulate, or be physically active can occur at any time during the continuum of care. However, early detection of challenges and intervention can prevent or minimize deterioration in nutrition status and quality of life through nutrition screening and the nutrition care process which includes nutrition assessment, diagnosis, intervention, and monitoring/evaluation [1]. It is equally important to monitor survivors for weight gain during treatment, given the high number of patients currently overweight or obese prior to beginning antineoplastic therapies.

The Institute of Medicine (IOM) has published the consensus report "From Cancer Patient to Cancer Survivor: Lost in Translation" that recommends a cancer survivorship plan designed for all cancer survivors, as many patients are left to fill in the gaps of "what to do next" when they finish treatment [48]. Moreover, non-oncology clinicians generally are not familiar with treatment-related side effects that often linger long after treatment has seized [1]. Given that the majority of American cancer survivors are either overweight or obese and sedentary, survivorship plans should target a reduction in excess energy intake to promote weight loss

Table 13.5 Summary of dietary link and major cancers

	Convincingly risk	Probably risk	Limited evidence suggests risk	Convincingly risk	Probably risk	Limited evidence suggests risk
Adult wt. gain					B (PM)	
Body fatness		B (PRM)		B (PM), C/R, EN, ES, K, PA	O	LI
Abdominal fatness				C/R	B (PM), EN	
Fruit/vegetable intake		ES, L (fruits), G	C/R, L/O (vegetables), LI/PA (fruit)			
High-fiber foods	C/R		ES			
Intake of simple sugars/ refined CHOs						Foods in sugar (C/R)
Red meat/processed meats				C/R		ES, G, L, PA, P
Alcohol				B (PM), C/R (men), ES, HNC	C/R (women), LI	
Physical activity	C/R	B (PM), EN	B (PRM), L, PA			
Other		Ca^{++} diet (C/R); foods lycopene (P)	Legumes (G); foods high in Se (G)	B-carotene supplements (L)	Glycemic load (EN); maté (ES); salt (G); diets in Ca^{++} (P)	Foods high in Fe^{++} (C/R); cheese (C/R); diets milk/dairy (P)

Abbreviations: *B* breast, *C/R* colon/rectal, *EN* endometrial, *ES* esophageal, *G* gastric, *HNC* head/neck, *L* lung, *LI* liver, *P* prostate, *PA* pancreatic, *PM* postmenopausal, *PRM* premenopausal, *O* ovarian, *Ca++* calcium, *Fe++* iron, *Se* selenium

in this patient population. Survivorship plans should be also designed to encourage cancer survivors to increase their daily activity levels depending on their baseline clinical status. Excess body weight and low physical activity levels are key modifiable risk factors for recurrence of common cancers such as that of the breast, prostate, endometrium, and colorectum [3, 4].

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Symptom Management: Weight Gain

14

Jennifer W. Bea, Hendrik D. De Heer, and Anna L. Schwartz

14.1 The Problem

Being overweight or obese, classified by body mass index (BMI) of 25–29.9 kg/m^2 and ≥30 kg/m^2, respectively, is considered a risk factor for several cancers. Approximately one-third of all cancers in the United States are related to patients being overweight or obese and physically inactive and consuming a diet poor in nutritional value [1, 2]. The cancers most often associated with obesity are postmenopausal breast cancer; colorectal, endometrial, kidney, pancreatic cancer, and the adenocarcinoma subtype of esophageal cancer. The risk of other cancer types has been inconsistently associated with obesity, such as prostate cancer [3–5].

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Many physicians, scientists, and the public are aware of the cancer risks associated with excess weight. It is less well known that post-diagnosis weight gain is associated with some cancers and cancer treatments. Although weight gain is common in some cancers, the risks associated with the weight gain are unclear. Some studies indicate that overweight, obesity, and weight gain are associated with poorer outcomes, including increased risk for recurrence, metastasis, poorer quality of life (QOL), and reduced survival for several types of cancers [2, 6–10], while others show no association between weight gain and recurrence or survival [11–13]. In addition, weight loss can also occur in cancer survivorship within the cancer types commonly associated with weight gain, although it may be less common. Weight loss can also be associated with poorer outcomes [13].

It appears that monitoring weight change and considering overall medical history and treatment are critical to providing advice regarding weight management in cancer survivorship. For example, poorer outcomes with weight gain may be due, in part, to decreased effectiveness of extended adjuvant endocrine-modulating therapies in obese survivors compared to normal weight survivors [14–17]. So, whether an individual is overweight or obese when diagnosed or experiences weight changes over the course of treatment, weight management can be an important component of supportive care.

This chapter will focus primarily on issues related to weight gain. First, we will review the evidence describing which cancers and cancer treatments are associated with weight gain. Research will be summarized detailing what cancer patients and survivors can do to prevent and treat weight gain, both during and after cancer treatment. In this section, behavioral strategies (such as modification of physical activity and dietary intake) and therapeutic and pharmacological approaches will be highlighted. In addition, surgical approaches and integrative approaches that combine several strategies will be discussed. It should be noted that the current body of literature related to cancer and weight gain is heavily weighted toward breast cancer research, and thus, this chapter is similarly skewed. The chapter will conclude with directions for future research in the area of weight gain and cancer prevention and treatment.

14.2 Evidence

Adverse changes in body composition, along with weight gain and weight loss, have been described among cancer survivors, both during and after treatment. Several of the most common cancers and cancer treatments have been associated with weight gain – the most commonly studied are breast cancer (including ductal carcinoma in situ) and colorectal cancers. Some evidence is available for prostate cancer, ovarian cancer, and some other less common cancers.

14.2.1 Breast Cancer

The majority of the research regarding risks associated with weight gain and cancer has been conducted among breast cancer survivors. These studies have found that weight gain following breast cancer diagnosis remains a significant concern, in spite of changes in cancer therapy. Evidence has suggested that post-diagnosis weight gain among breast cancer survivors is associated with functional limitations, pain, decreased QOL, and poorer survival particularly among racial/ethnic minorities. However, not all study findings have been consistent, as described below [12].

14.2.1.1 Prevalence of Weight Gain

A 2011 review by Vance and colleagues [18] including 32 studies reported that between 50 and 96 % of women experience weight gain during treatment for breast cancer, and many (including some who did not gain weight during treatment) have reported weight gain during the months after diagnosis.

The earliest studies reported a high proportion of patients gaining weight. For example, the oldest study in the review by Haesman and colleagues reported that 96 % of a sample of 237 women treated with adjuvant chemotherapy gained weight during treatment [19]. In 1986, Chlebowski and colleagues reported that among 62 women receiving adjuvant chemotherapy, 91 % of CMF-treated women reported weight gain and 74 % of 5-FU-treated patients [20].

Although lower than the initial studies, more recent, larger studies report that substantial proportions of patients gained weight during and after treatment. The study with the largest number of participants was the Nurses' Health Study, which included 5204 participants diagnosed with incident, invasive, nonmetastatic breast cancer [21]. In this study, it was found that about half experienced post-diagnosis weight gain, whereas 21.5 % reported weight loss. The weight gain or loss was defined as the weight change from pre-diagnosis to first measured BMI at least 12-month post-diagnosis. The second largest study ($N = 3993$) of women diagnosed with invasive nonmetastatic breast cancer found that 70 % of participants gained at least 2 kg. The average follow-up from diagnosis was 5.8 years [22].

14.2.1.2 Amount of Weight Gain

The mean amount of weight gain for the entire study population ranges from 0.30 kg among a study of 260 Korean women [23] to 5.0 kg among 17 patients in early-stage breast cancer receiving adjuvant chemotherapy [24]. Most studies reported a weight gain of about 2–3 kg on average, with a follow-up period of about 3 years. For example, Rock and colleagues found that among 1116 stage I–IIIA breast cancer patients who had completed adjuvant chemotherapy and/or antiestrogen treatment, average weight gain was 2.7 kg over a 26-month period [25]. A large study ($N = 3250$) by Cann et al. reported that mean weight gain over the study period (median follow-up of 5 years) was 2.4 kg [11].

14.2.1.3 Factors Associated with Weight Gain

Several factors have been identified to be associated with weight gain. First, several studies tracked weight at different time points and found that weight gain increased in the years after follow-up. For example, in a study of 185 stage I–III breast cancer patients receiving adjuvant chemotherapy and/or hormonal therapy, Makari-Judson and colleagues reported that average weight gain in the first year was 1.5 kg, at 2 years 2.7 kg, and at 3 years 2.8 kg [26]. Levine and colleagues reported that for 69 % of breast cancer patients receiving adjuvant therapy ($N=32$), weight gain during treatment averaged 1.8 kg, whereas at 2-year follow-up, 84 % had gained weight with an average of 4.18 kg [27]. Caan and colleagues further reported that in their study of 3250 patients in stage I–IIIA breast cancer, weight gain was progressive after diagnosis in all treatment groups, but stabilized at about the 3-year follow-up time point [11].

Another factor that may impact weight gain and its consequences is whether patients treated were premenopausal or postmenopausal. Several studies have reported that weight gain during and after treatment was greater among premenopausal women compared to women who were postmenopause. In a study of 646 patients with node-positive disease treated with or without adjuvant chemotherapy, Camoriano and colleagues found that premenopausal women gained an average of 5.9 kg at a median follow-up of 6.6 years, compared to 3.6 kg for postmenopausal women who were treated with adjuvant chemotherapy [28]. Women who were postmenopause and did not receive adjuvant chemotherapy only gained an average of 1.8 kg. Consistent with these findings was a recent study by Heideman and colleagues among 271 Dutch women with stage I–III breast cancer who received chemotherapy and/or hormonal therapy (71 %) or no systemic treatment (29 %). At the follow-up (mean 3.1 years), it was found that on average, premenopausal women gained 3.9 kg, compared to 1.1 kg of postmenopausal women [29]. However, findings are not all consistent, as a small study by McInnes and Knobf ($N=44$) reported little difference in weight gain between premenopausal and postmenopausal breast cancer patients at 1- and 2-year follow-up (although from 2–3-year follow-up, postmenopausal women gained 1.5 kg on average, compared to 0.4 kg among premenopausal women) [30]. These effects may further be impacted by age. For example, in a large study ($N=1116$), Rock and colleagues reported that postmenopausal breast cancer patients over the age of 50 gained on average 2.0 kg, compared to 2.4 kg for premenopausal women. However, women who were postmenopause and *under 50* gained an average of 4.5 kg [25].

The most recent study of weight changes in breast cancer survivors ($N=665$) confirmed the factors associated with weight gain in breast cancer survivorship above as well as adding some additional insight. The study evaluated up to 5-year post-diagnosis weight changes to determine patterns and influencing factors. The mean weight gain was 4.5 % ± 10.6 % body weight; a total of 44 % of women gained at least 5 % body weight. Older age again conferred slightly lower risk of weight gain ($OR_{adj}=0.97$, 95 % CI 0.95–0.99), as did Hispanic ethnicity ($OR_{adj}=0.30$, 95 % CI 0.13–0.68). Being overweight ($OR_{adj}=0.11$, 95 % CI 0.05–0.23) or obese

(OR_{adj} = 0.03, 95 % CI 0.02–0.07) at diagnosis was also inversely associated with weight gain. Time elapsed since diagnosis (OR_{adj} = 1.19/year, 95 % CI 1.04–1.36) and smoking at diagnosis (OR_{adj} = 2.69, 95 % CI 1.12–6.49) were positively associated with weight gain [31].

14.2.1.4 Weight Gain and Disease-Free Survival

Most studies evaluating the impact of weight gain on breast cancer treatment outcomes have included disease-free survival, generally defined as cancer recurrence and mortality. Additionally, several studies have evaluated the impact of weight change on functional abilities, quality of life, and pain.

In several large studies, weight gain during and after treatment has been associated with poorer disease-free survival. In the Nurses' Health study (N = 5204), the authors contrasted those who maintained their weight (median weight change 0.0 lbs) to participants who lost weight (median 9.0 lbs) and those who gained weight (median 6.0 lbs) and participants who gained a substantial amount of weight (median 18.0 lbs). They found that among participants who never smoked, at follow-up (median 9 years), weight gain (but not weight loss) was significantly associated with higher all-cause mortality, breast cancer deaths, and cancer recurrence. Greater weight gain was associated with greater risk of recurrence and mortality [21].

These findings are consistent with another large recent study (Nichols et al. 2009) of 3993 women with invasive nonmetastatic breast cancer. The authors found that each 5 kg weight gain was associated with an increased risk of all-cause (RR = 1.12) and breast cancer mortality (RR = 1.13). Weight gain of greater than 10 kg was associated with a 70 % and 78 % increased risk, respectively [22]. Not all findings are consistent, however, as other large studies did not find an association between weight gain and recurrence or mortality. A study of 1692 breast cancer survivors followed for up to 4 years demonstrated that weight gain after a breast cancer diagnosis was not associated with an increased risk of recurrence or death from any cause; additionally moderate weight loss (5–10 %) did not decrease risk of these outcomes [12]. Similarly, risk of recurrence was not associated with weight gain in breast cancer survivors followed for 5–7 years [11]. Yet, other factors may influence the results, for example, Camoriano et al. only found an association of premenopausal women between weight gain and recurrence and mortality [28].

14.2.1.5 Weight Gain and Functional Outcomes

Weight gain during and after treatment has further been associated with other treatment outcomes such as functional limitations and pain. In a large, recent, cohort of early-stage breast cancer survivors (N = 1841), post-diagnosis weight gain ≥10 % was associated with an increase in any limitation (OR = 1.79; 95 % CI = 1.23–2.61), moderate to severe limitations (OR = 2.30; 95 % CI = 1.75–3.02), and lower body limitations (OR = 2.05; 95 % CI = 1.53–2.76) compared to women who maintained weight within 5 % of pre-diagnosis weight [32]. In another recent study, even less weight gain (≥5 %) was associated with lower scores in physical functioning

(−7.2 %) and vitality (−11.2 %) among breast cancer survivors ($N=483$; all P trend <0.05) [33]. The association between functional limitations and weight loss is less clear. Significant weight loss (≥10 % pre-diagnosis weight) among normal weight women without comorbidity and overweight/obese women with a comorbidity may increase the risk of functional limitations, but significant weight loss in overweight/obese women without comorbidities was associated with a lower risk of limitations [32]. Preventing functional limitations may be best achieved by supporting weight maintenance during and after breast cancer therapy.

Post-diagnosis weight gain (>5 %) has also been positively associated with above-average pain determined by SF-36 bodily pain scores (OR, 95 % CI = 1.76, 1.03–3.01, above average = bodily pain scores ≥1/2 standard deviation worse than age-specific population norms). Physical activity may mitigate the pain, but a large randomized controlled trial specifically designed to test the effects of physical activity on pain and other symptoms in breast cancer survivors who have experienced significant post-diagnosis weight gain has not yet been conducted [34]. There is some indication that the negative impact of endocrine-modulating therapies on body habitus, pain, and QOL may be ameliorated by physical activity in premenopausal breast cancer survivors based on a small feasibility study ($N=41$) [35].

14.2.2 Colorectal Cancer

Given the prevalence of colon cancer and the established increased risk for colon cancer among the overweight and obese [3], there is a surprising gap in the state of knowledge related to weight status and weight gain during survivorship. Among resected colon cancer patients, some recent evidence suggests that being overweight or obese may be associated with poorer prognosis compared to being of normal weight [36]; however, the relationship may not be linear and may be geographically specific. For example, one large prospective study by Meyerhardt reported that weight change during the time period between ongoing adjuvant therapy and 6 months after completion of therapy did not significantly impact recurrence and survival among 1053 patients with stage III colon cancer, although 64.3 % of participants reported a weight gain of 5 kg or more and 76.8 % of participants reported a weight gain of at least 2 kg. Less than 10 % of participants reported a weight loss greater than 2 kg. However, the data revealed that the pattern of the chances of cancer recurrence was quadratic, with people losing or gaining a lot of weight having the highest hazard ratios and the people maintaining their weight having the lowest hazard ratios [37]. Meanwhile, another recent study in Taiwan demonstrated no effect of overweight or obese status on survival outcomes [38]. The differences between studies may be partially explained by tumor characteristics. For example, tumor expression of p27 [39] and p21 [39] has been shown to interact with body mass index to influence prognosis and survival. Further, exercise post-diagnosis has been associated with improved survival among colon cancer survivors [40], which may be partially influenced by the positive changes in body composition induced by exercise.

14.2.3 Prostate Cancer

The effects of obesity on prostate cancer are varied. The differences between earlier studies may have been due to obesity increasing the risk of aggressive prostate cancer, but reducing the risk of low-grade, nonaggressive, and more treatable cancer, which has been made evident more recently [41, 42]. Recent reviews suggest that overweight or obesity status may also increase the risk of recurrence in prostate cancer patients [36, 41], and the larger individual studies support the notion that obesity prior to diagnosis leads to poorer outcomes post-diagnosis. For example, the prospective National Institutes of Health-AARP Diet and Health Study demonstrated an increased risk of prostate cancer mortality, but not incidence with higher BMI and adult weight gain among the 287,760 men ages 50–71 years followed for 5–6 years [5]. Similarly, the recent Physicians' Health Study analysis of men diagnosed with prostate cancer ($N=2546$) followed for approximately four times as long (24 years) showed that overweight and obese men had a significantly higher risk of prostate cancer mortality (proportional hazard ratio [HR] 1.47 [95 % CI 1.16–1.88] and 2.66 [1.62–4.39], respectively; $P(\text{trend})<0.0001$), which remained even after controlling for clinical stage and Gleason grade. In a subgroup analysis, overweight/obese status with high C peptide concentrations conferred four times higher risk of mortality (4.12 [1.97–8.61]; $P(\text{interaction})=0.001$) [43].

Joshu et al. demonstrated nearly double the risk of prostate cancer recurrence with weight gain >2.2 kg from the years prior to prostatectomy to the years postsurgery [44]. Another very recent analysis by Bonn et al. of weight status at diagnosis as well as weight change and prostate cancer progression and survival was conducted in $N=4376$ men diagnosed with localized prostate cancer, confirming increased risk of all-cause mortality among men who were obese at diagnosis (HR 1.47, 95 % CI 1.03–2.10). Further, the post-diagnosis weight change analysis demonstrated a U-shaped relationship, such that weight loss >5 % after diagnosis almost doubled the rate of all-cause mortality (HR 1.94, 95 % CI 1.41–2.66), and weight gain >5 % nearly doubled the rate of prostate cancer-specific mortality (HR 1.93, 95 % CI 1.18–3.16), compared to maintaining a stable weight [45]. However, the influence of adult weight gain prior to diagnosis remains unclear [42, 46, 47].

Several studies have documented that men diagnosed with prostate cancer experience adverse changes in body composition during and after treatment. These changes appear to be strongly related to androgen deprivation therapy and other treatments that will be discussed more in depth within Sect.14.2.9.

14.2.4 Gynecologic Cancers

14.2.4.1 Ovarian Cancer

One of the largest prospective studies, the European Prospective Investigation into Cancer and Nutrition (EPIC, $N=226{,}798$ women) confirms the suspected relationship between obesity and risk epithelial ovarian cancer [48], although the relationship may vary by early adulthood weight status and pre- versus postmenopausal

diagnosis, even after accounting for age of menarche [49]. Further, obesity may delay diagnosis, interfere with surgical and cytotoxic treatment, and increase complications [50], yet there is little information on the impact of weight status at diagnosis and weight gain following diagnosis. In general, it appears that weight change (increase or decrease) during and after treatment for ovarian cancer may be stage specific [51], but overall, post-diagnosis weight gain has been identified as a concern among ovarian cancer survivors themselves [52]. As such, a panel of experts from the National Cancer Institute recommends evaluating weight gain in ovarian cancer clinical trials [53]. Given the limited evidence, the association between mortality and high BMI and weight gain is unclear, for example, Backes et al. found no effect of BMI on overall survival in a study of 198 patients, but a nonsignificant trend toward increased risk of death with weight gain over the 6-month posttreatment period [54], while Zhou et al. found that post-diagnosis BMI was significantly associated with ovarian cancer mortality, as was adult weight gain, in a study roughly twice the size [55]. One reason for disparate outcomes may be weight gain and resolution due to water retention with treatment, which should be distinguished from changes in body composition related to fat mass, lean mass, and bone [56].

Of note, there is some evidence that diet may influence overall survival among ovarian cancer patients [57]; however, trials to prevent weight gain or promote weight loss among ovarian cancer survivors are lacking. Two ongoing trials to determine if healthy lifestyle may influence survival in ovarian cancer will likely shed light on outcomes related to weight change, as well. The trials are described in Sect. 14.3.

14.2.4.2 Endometrial/Uterine Cancer

Endometrial cancer of the uterus is the most common gynecologic cancer. Body mass and degree of fat mass have been associated with risk of endometrial/uterine cancer [3, 58], with early life exposure to high BMI and weight gain contributing to higher risk and earlier onset [59]. Although the majority of women are diagnosed with early stage-disease, obesity-related comorbidities, such as cardiovascular disease, may be contributing to overall mortality, as up to 70 % of these patients may be obese today [7, 60]. However, there is a paucity of research related to body habitus and disease outcomes following endometrial cancer diagnosis [7, 60], the studies that are available are not aligned in design or outcome. The first reviewed study demonstrated that BMI was associated with all-cause mortality and complications, but not disease-specific mortality or cancer recurrence among early-stage uterine cancer patients ($N=2596$ women) [61]. In contrast, another study found no association between obesity and overall survival [62], and yet another found moderate weight gain 6 months after diagnosis to be associated with the best prognosis. The worst prognosis was among those with weight loss which persisted when the analysis was restricted to recurrences at follow-up >18 months. In a relatively large trial limited to obese patients ($N=659$; BMI obese 30–39 kg/m^2, morbidly obese 40–49 kg/m^2, and super obese ≥50 kg/m^2, respectively) with endometrial hyperplasia/uterine cancer, the degree of obesity did not influence progression-free or disease-specific survival, but did influence surgical outcomes in those

with a BMI ≥40 kg/m^2 [63]. Based on the small amount of evidence, targeting lifestyle changes and weight maintenance may be the best course of action in endometrial cancer patients who are not morbidly obese. Recent lifestyle interventions among obese endometrial cancer survivors have shown that significant intentional weight loss and improved lifestyle behaviors are feasible in this population [64, 65], but clinical outcomes are not yet known and will require larger randomized controlled trials.

14.2.5 Other Cancers

There is very little literature on the topic of post-diagnostic weight gain and cancer outcomes for thyroid cancer and lymphoma. The limited amount of evidence is summarized here.

Risk of thyroid cancer has been associated with high adult BMI, weight gain, and fat distribution [66, 67]. Post-diagnosis, one study found no differences in weight gain over time between patients with thyroid cancer receiving thyroidectomy and a control group of euthyroid patients with thyroid nodules or goiter [68]. Another study that included thyroidectomy due to multiple causes found that thyroidectomy may be associated with increased body weight [69]. Despite the lack of clear evidence for thyroid cancer outcomes of QOL, prognosis, and survival related to body weight, thyroid-stimulating hormone levels are dependent on body weight, and medications should be titrated accordingly [70].

Higher weight and BMI in early adulthood have been associated with non-Hodgkin lymphoma risk [71]. Although non-Hodgkin lymphoma patients may be prone to weight gain and adverse body composition changes with treatment [72], the effects of weight change on QOL, prognosis, and survival are unclear for this cancer, as well. Among non-Hodgkin lymphoma patients, being underweight at diagnosis or any pre- or post-diagnosis or treatment weight changes were associated with poorer survival in one study (underweight HR = 2.84; 95 % CI = 1.12–7.15; pre-diagnosis weight loss HR = 1.42; 95 % CI = 1.02–1.97; posttreatment weight loss HR = 1.98; 95 % CI = 1.14–3.45; post-diagnosis weight gain HR = 1.85; 95 % CI = 1.04–3.32) [73], while posttreatment weight gain was associated with a positive prognosis in another study [74].

14.2.6 Cancer Treatments Associated with Weight Gain

Some chemotherapies and endocrine modulating therapies have been associated with weight and body composition changes. Sex steroids play a significant role in body weight and body composition regulation. Cancer treatments that limit or eliminate circulating sex steroids such as estrogen, testosterone, and dihydroepitestosterone (DHT) have been associated with weight gain; these include pharmaceutical blockade, ovarian and testicular failure, and/or gonad removal.

14.2.7 Chemotherapy

Adjuvant chemotherapy has been implicated in weight gain among breast cancer survivors in the United States and Europe as well as the promotion of sarcopenic obesity (preferential gain of fat and loss of lean body mass) in both chemotherapy-induced ovarian failure patients and naturally postmenopausal breast cancer survivors, although pretreatment weight and menopausal status may modify the relationship between chemotherapy and body composition and weight changes [10, 75–77]. Other regions do not experience weight gain with chemotherapy, which may be attributable to differences in age of diagnosis, initial body weight, therapeutic regimens, environment, and behavior [78, 79]. Whether or not the weight gain resulting from chemotherapy in breast cancer directly results in poorer outcomes is not clear. Results from the large Nurses' Health Study ($N=5204$) suggest that weight gain may significantly increase the risk of breast cancer recurrence [21], while results from other observational studies have been mixed [11, 80]. However, other prognostic outcomes in breast cancer patients, including overall survival and new cancers, that may be related to post-chemotherapy weight gain have not been sufficiently evaluated. The effects of chemotherapy on weight in other cancer survivor populations await further study.

14.2.8 Estrogen Modulation in Women

In addition to loss of ovarian function either from chemotherapy or simply natural menopause, extended endocrine-modulating therapies, such as selective estrogen receptor modulators (SERM), aromatase inhibitors (AI), or estrogen receptor blockers, are administered to reduce recurrence and improve overall survival in breast cancer survivors, with choice of medication depending on menopausal status [81]. Tamoxifen, an SERM, often given to breast cancer survivors, has long been associated with increased body weight [82] and more recently associated with increased body fat, fatty liver, and intra-abdominal fat [83, 84]. Aromatase inhibitors, which act to reduce the availability of estrogen, were less likely to be associated with weight gain than SERMs ($OR_{adj}=0.54$, 95 % CI 0.31–0.93) [31], and women who switched from SERMs to AIs experienced a favorable shift in body composition up to 24 months due to decreases in body fat ($P<0.05$) and increased lean body mass [85, 86]. Fulvestrant, an agent that competitively binds estrogen receptors, may be employed for tamoxifen-resistant, estrogen-sensitive, human breast cancers; however, there is insufficient evidence in the literature to determine if luteinizing hormone-releasing hormone (LH-RH) agonist or estrogen receptor blocker (fulvestrant) therapies contribute to weight gain, although the common biological mechanism of limiting circulating estrogen implies that they may.

14.2.9 Antiandrogen Therapy in Men

Androgen deprivation therapy (ADT) is associated with weight gain and adverse changes in body composition in men being treated for nonmetastatic prostate cancer [87–91]. Similar to weight gain in breast cancer survivors, the weight gain in prostate cancer survivors varies by baseline age and BMI. Those <65 years of age or a BMI <30 kg/m^2 treated with leuprolide were more likely to gain weight in a recent study of nonmetastatic prostate cancer survivors treated with ADT for at least 6 months ($N=118$) [89]. Additionally, smaller studies of men with nonmetastatic prostate cancer treated with the GnRH agonist leuprolide ($N=32$) or either GnRH agonist or bilateral orchiectomy ($N=79$) had significant increases in body weight and percentage fat body mass and decreases in percentage lean body mass and muscle size [88, 92]. Of note, the increased body fat was primarily a result of subcutaneous rather than intra-abdominal fat [88]. A prospective study of age- and education-matched prostate cancer survivors on ADT, prostate cancer survivors not on ADT, and healthy controls followed for 3 years ($N=257$) confirmed that prostate cancer survivors on ADT gained significantly more weight than those not using ADT and healthy controls. It also demonstrated greater weight gain in those <65 years of age ($P=0.005$) [93]. Although counterintuitive, it may be that the younger, healthier prostate cancer survivors are in greater need of weight management counseling than older survivors.

Further, Hakimian et al. reported that ADT has been prospectively linked to increased high cholesterol and triglycerides, insulin resistance, and metabolic syndrome [94], which are biomarkers commonly associated with obesity and weight gain. As a result, Saylor and Smith report that ADT has been associated with an increased risk of diabetes and cardiovascular disease [94–97]. Again, exercise has been associated with decreased cancer-specific mortality among prostate cancer survivors, and known positive effects of exercise on body composition may account for a portion of the association [40].

14.2.10 Changes in Body Composition

Even without weight gain, unfavorable changes in body composition (i.e., decrease in lean muscle mass, fat gain, bone density changes) have been found to be prevalent. Several studies have documented that fat mass has increased and represents most of the weight gain during and after breast cancer. A recent review by Vance et al. indicated that breast cancer patients stages 0–III may gain about 2 kg in fat mass at 6 and 12 months follow-up, representing an approximate increase in body fat of 2 %; a similar 2 % increase in body fat was also found between the first- to third-year post-diagnosis in another study. Other unfavorable changes have included a decrease up to 4 % of fat-free mass, especially pronounced in the leg region, and a decrease in bone mineral density [18].

Sarcopenia, the degenerative loss of skeletal muscle, is commonly found among cancer patients. For example, the Health, Eating, Activity and Lifestyle (HEAL) study enrolled 1183 women with breast cancer who were within 12 months of diagnosis. In a sub-analysis, 471 women with invasive ductal carcinoma had a *dual-energy X-ray absorptiometry* (DXA) scan 12 months post-diagnosis and were followed for 9 years; of these women, 75 (16 %) were sarcopenic and 38 % were obese. Women with sarcopenia were older at diagnosis and had lower body fat, smaller waist circumference, and lower BMI compared to nonsarcopenic women. Sarcopenic women were postmenopausal and diagnosed with earlier stage of disease. Sarcopenia was associated with an increase risk of all-cause mortality and a higher cancer-specific mortality and shorter survival compared to nonsarcopenic survivors [98].

Sarcopenia is strongly associated with adverse outcomes (treatment toxicity and poorer survival) in other cancers too [99]. Low skeletal muscle mass is associated with greater chemotherapy toxicity in colon cancer patients ($N=62$) receiving 5-FU and leucovorin, with women having a higher odds ratio for toxicity (OR, 16.73; $P=0.021$) [100]. Obese sarcopenic patients with gastrointestinal or lung cancer ($N=250$) also have a higher risk of mortality (HR = 4.2; 95 % CI, 2.4–7.2) compared to nonsarcopenic patients [101]. In the pancreatic setting, sarcopenia predicts mortality among overweight and obese patients ($N=111$) (HR = 2.07; 95 % CI, 1.23–3.50) [102].

Taken together, these findings indicate that unfavorable changes in body composition including lean mass, fat percentage, and bone density are prevalent among most cancer patients/survivors. The absence of weight gain does not preclude cancer survivors from experiencing adverse consequences based on changes in body composition.

14.2.11 Weight Loss

Although the focus of this chapter is on weight gain, it should be noted that weight loss can be a significant problem in breast cancer survivorship, as well. A recent pooling project by Caan et al. with more than 12,000 participants supported the prior literature on increased risk of death with weight gain, although it did not reach significance. However, while fewer women lost weight than gained it, 14.7 % versus 34.7 %, the study participants who lost ≥10 % were at a 40 % increased risk of death in the United States and greater than 3 times the risk in Shanghai ($P<0.05$) [13]. These results imply unintentional weight loss due to recurrence. Additionally, pre-diagnosis weight status was a mediating factor, as were comorbidities [13]. Unintentional weight loss is also associated with poorer outcomes and survival in various advanced cancers, such as colon, head and neck, ovarian, and others [103–106]. Taken together, weight stability throughout treatment and survival is optimal and individual medical history should inform on the type of weight management advice given to cancer patients and survivors.

14.3 Ongoing Research

Several studies funded by the National Cancer Institute (NCI) are underway to examine lifestyle interventions for weight management in cancer survivorship. Additionally, there are both core centers (P30) and research consortia (U54) funded by the NCI that include weight management pilot and full projects. The following paragraphs describe a few NCI trials funded at the R21 and R01 level that are underway; it is in no way an exhaustive list of clinical trials. Nevertheless, great strides are expected to be made in the field in the coming decade.

14.3.1 Individual Cancer Types

As noted earlier in the chapter, current interventions are more heavily weighted toward breast cancer survivors. However, trials incorporating other cancer types and underserved populations within breast cancer are underway and will lead to advances in the literature and perhaps the standard of care for survivors. Dr. Cheryl Rock is leading a multidisciplinary trial named "Reducing Breast Cancer Recurrence with Weight Loss: A Vanguard Trial" from the University of California, San Diego, but the trial joins experienced investigators from five of the leading cancer centers. Along with primary and secondary aims related to weight loss maintenance, cost-effectiveness, QOL, and mechanisms, the ultimate goal of the trial is to initiate the effort to establish weight control support for breast cancer survivors as a new standard of clinical care. The project is expected to be completed by February 2015. Another study to explore the efficacy of a weight loss intervention on BMI, biological markers of breast cancer progression, comorbidities, and psychosocial factors among breast cancer survivors will incorporate the underserved African American population. The trial is led by Dr. Melinda Stolley at the University of Illinois in Chicago. The project is expected to come to a close in July of 2016. To better understand and serve rural breast cancer survivors, Dr. Befort at the University of Kansas Medical Center is leading a group phone-based intervention for weight control among rural breast cancer survivors. The purpose of the study is to develop a clinically effective and cost-efficient strategy for producing long-term weight loss maintenance, associated biomarker modulation, and improved quality of life among rural breast cancer survivors who are at greater risk for recurrence than their urban counterparts. The project is expected to end in May of 2016. Additionally, ductal carcinoma in situ (DCIS) will be used as a model to explore mechanisms by which obesity and weight loss may affect neoplasia by Dr. Wendy Demark-Wahnefried at the University of Alabama in Birmingham. The trial is exploring the feasibility and potential impact of presurgical weight loss on serum biomarkers, tumor characteristics, and clinical outcomes of overweight and obese patients with DCIS. The planned completion date is March 2016.

The less studied ovarian cancer survivor population will contribute to two large trials that have been recently initiated to examine the effects of diet and physical activity in ovarian cancer. Although weight loss is not the primary aim of either

trial, useful information about weight management in the context of ovarian cancer is likely to emerge. The "Impact of Exercise on Ovarian Cancer Prognosis" study (PI: Dr. Melinda Irwin) will enroll women diagnosed with stage I–III ovarian cancer ($N = 230$). Women will be randomly assigned to 6 months of moderate intensity aerobic physical activity, at 150 min per week, or attention control. The primary outcomes are QOL and surrogate markers of prognosis. The LIvES (Lifestyle Intervention for Ovarian Cancer Enhanced Survival; PI: Dr. David Alberts) study is a randomized trial of recent stage II–IV ovarian, primary peritoneal, and fallopian tube cancer survivors from among the Gynecologic Oncology Group (GOG) clinics across the United States ($N = 1070$). It will evaluate whether diet and physical activity combined can improve QOL and prevent recurrence for women who are in clinical complete remission from advanced ovarian peritoneal or tubal cancer.

A trial by Dr. Nora Nock at Case Western Reserve University will expand the research base for obese endometrial cancer (EC) survivors by evaluating a novel transdisciplinary approach to improve self-reported eating behavior, exercise motivation, and quality of life as well as decreased neural activation in response to high-calorie food images in brain regions associated with food reward and motivation among obese EC patients. The ultimate goal is improved survival of obese EC patients. This recently initiated project is not expected to be completed until 2018.

The National Cancer Institute of Canada Clinical Trials Group funds an ongoing exercise and colon cancer survivorship trial. This Colon Health and Life-Long Exercise Change trial will utilize a multi-site, structured physical activity intervention compared to general health education materials. The intervention will include supervised physical activity sessions and behavioral support over 3 years with the primary end point of disease-free survival. The team will also evaluate multiple patient-reported outcomes, objective physical functioning, biological correlative markers, and an economic analysis [107].

14.3.2 Multiple Cancer Types

In recent years, there has been some debate over whether or not to group various cancer types in cancer survivor studies. Trials of obesity-related cancers, such as colon and breast, with the common goal of weight management to improve survival have begun to combine populations. The following are two examples of such ongoing trials.

A trial of weight loss in female cancer survivors of colon and breast cancer, led by Dr. Heather Greenlee at Columbia University Health Sciences Center, will assess the feasibility of conducting a weight loss intervention for breast and colorectal cancer survivors in the Southwest Oncology Group (SWOG) using the Curves weight loss program plus telephone-administered behavioral counseling. The expected project end date is June 2015. In addition, the Promoting Weight-Loss in African American Cancer Survivors in the Deep South Study, led by the University of Alabama at Birmingham by Dr. Baskin, will evaluate multilevel weight loss interventions for African American cancer survivors, of multiple

cancer types, living in the rural Deep South. The study will add geographic and racial diversity to a limited evidence base in survivorship and may decrease risk for cancer recurrence and cancer-related mortality and improve quality of life in the African American survivor population. The expected completion date is March 2017.

14.4 Solutions

Although a growing body of research has shown changes in body composition among cancer survivors, a relatively small number of studies have evaluated approaches for prevention or reversal. Modifying strategies including lifestyle interventions and surgical or pharmaceutical approaches have been suggested to prevent weight gain or achieve weight loss among cancer survivors. Additionally, favorably modifying the body composition (i.e., fat and lean body mass) should be considered a positive outcome, in addition to or independent of weight loss because stable body weight can mask deleterious changes in lean body mass (i.e., muscle) and adipose with aging [10, 108–111].

14.4.1 Prevention of Weight Gain

The periods of diagnosis, treatment, and following treatment are key times that survivors seek self-management strategies to improve their health. These time periods are referred to as "teachable moments" and are key times to identify and present interventions for weight loss [112–115]. Lifestyle modification, including diet, exercise, and behavioral change, is the most commonly recommended approach for weight loss [116]. Lifestyle change may be the optimal approach to weight loss and certainly the approach with fewest adverse effects (no side effects from medications or risk of surgical complication). Cancer survivors are at risk for second malignancies, comorbidities related to being overweight or obese (diabetes, hypertension, CVD), and recurrence. Lifestyle changes that include improved diet, physical activity, and weight loss may not only provide a protective benefit but may improve QOL [117]. While key intervention time periods have been identified, there are limited evidence-based interventions specific to preventing weight gain in cancer survivors during and after cancer treatments. In addition, of the limited available evidence, the majority of studies have focused on women with breast cancer.

14.4.2 Preventing Weight Gain During Cancer Treatment

Strategies to prevent weight gain during cancer treatment have generally been based on recommendations for the general population. During treatment, the clinical goal

is to cure or control the cancer, and little attention may be given to controlling body weight. Clinicians generally encourage patients to control their weight and try not to gain weight during treatment. While specific guidelines do not exist for preventing weight gain during treatment, it is safe to recommend weight loss of up to 2 lb per week in breast cancer patients who are overweight or obese [118].

In addition, more clinicians are becoming aware of the benefit of exercise during treatment and are encouraging their patients to exercise, which has the added benefit of helping them to maintain their body weight [119]. It is difficult to recommend or encourage weight loss during treatment when the patient is under extreme stress and often doesn't feel well. But advising patients to increase physical activity and focus on healthy eating is sound advice that not only may help prevent weight gain but will have beneficial physical and psychological effects.

A small number of studies have evaluated the impact of lifestyle interventions on the prevention of weight gain during cancer treatment. These studies included exercise protocols or dietary interventions and have shown beneficial effects.

A study of 78 newly diagnosed women with breast cancer receiving chemotherapy followed a home-based 12-week aerobic exercise program. Women who adhered to the intervention maintained their body weight, while the non-exercisers gained a statistically significant amount of weight [120]. A pilot study of 12 patients with melanoma receiving interferon-alpha noted that patients who exercised and took methylphenidate maintained their body weight and did not lose weight, as is the concern with methylphenidate [121].

A recent trial by Villarini and colleagues randomized 96 breast cancer patients who received adjuvant chemotherapy into two dietary groups. The intervention group received a diet that combined Mediterranean and macrobiotic recipes and had an estimated caloric reduction of 250 cal/day. The control group only received baseline dietary recommendations. At both follow-up times (at the end of the first chemotherapy cycle and at the end of the treatment), it was found that intervention group participants lost significantly more weight (on average 2.9 kg more) and reduced their waist and hip circumference as well as fat mass [122]. Similarly, Goodwin et al. were able to induce significant weight loss among breast cancer patients receiving adjuvant chemotherapy ($N=338$) through diet- and exercise-based lifestyle intervention with telephone-based support; weight loss was maintained at 24-month follow-up, and the intervention did not adversely effect medical events, QOL, or hospitalizations [123]. Unfortunately the trial was underpowered to examine disease-free survival, due to early termination from loss of funding. Randomized controlled trials with long-term follow-up, which are adequately powered to detect lifestyle influences on morbidity and mortality, are required to determine if weight loss or prevention of weight gain in this setting is truly beneficial.

14.4.3 Preventing Weight Gain After Cancer Treatment

Weight gain following chemotherapy is associated with sarcopenic obesity. Sarcopenic obesity is weight gain with the concurrent loss of lean tissue. Overweight,

obesity, and sarcopenia may be independent predictors of morbidity and mortality in cancer survivors [98]. Although there is a growing body of research to suggest that weight gain following cancer treatment increases risks for recurrence and development of comorbid conditions, few studies have examined the efficacy of weight gain prevention strategies after treatment, which include lifestyle change, pharmacological approaches, and surgery.

14.4.4 Weight Loss After Treatment: Behavioral Interventions

14.4.4.1 Physical Activity: Aerobic Training

Studies have consistently demonstrated the benefits of physical activity on a range of outcomes among cancer survivors. These benefits have been demonstrated for both aerobic activity and resistance training. A systematic review of 14 randomized trials by McNeely and colleagues reported that physical activity had a beneficial impact on physical functioning, QOL, and oxygen uptake. The authors further found evidence that exercise reduced cancer fatigue [124].

Several studies have shown a beneficial effect of physical activity on body composition. For aerobic activity, an example includes the Yale Exercise and Survivorship Study (YES study), which followed 75 inactive postmenopausal breast cancer survivors randomized to "usual care" or to "exercise aerobically for 150 minutes/week" for 6 months. Women in the exercise arm increased their activity by 129 min/week compared to 45 min/week among usual care participants. The study further found statistically significant decreases in percent body fat and increases in lean mass and bone mineral density compared to the usual care arm. Women who exercised more demonstrated greater losses in body fat [125].

14.4.4.2 Physical Activity: Resistance Training

In women with breast cancer, sarcopenic obesity has been associated with reduced physical activity and suggests that exercise interventions, specifically resistance exercise for the lower body, may prevent weight gain [76].

Indeed, resistance training has been shown to have positive impacts on body composition. A randomized study of 85 breast cancer survivors that engaged in 6–12 months of resistance training two times per week resulted in significant increases in lean mass and decreases in % body fat [126]. A similar randomized trial of 106 postmenopausal breast cancer survivors at least 1-year posttreatment demonstrated that women in the resistance plus impact exercise intervention had greater increases in lean mass as measured by DXA scan [127]. There were no differences in body fat mass or percent body fat, but the increase in lean mass was more pronounced among survivors taking aromatase inhibitors compared to controls not on an aromatase inhibitor. Aromatase inhibitors increase free testosterone and lean mass possibly through a synergistic effect with resistance exercise.

Another study consistent with these findings compared the effects of land-based versus water-based exercise among a group of 98 breast cancer survivors. The study

demonstrated that land-based exercisers had lower body fat and lean body mass than breast cancer survivors who exercised in the water [128]. Land-based, weight-bearing exercise is important to maintain lean body mass and preserve bone density.

14.4.4.3 Dietary Interventions

Several diet and weight loss interventions have been conducted. The Women's Intervention Nutrition Study (WINS) and the Women's Healthy Eating and Lifestyle (WHEL) studies were conducted with early-stage breast cancer survivors and examined the effects of diet changes on recurrence and survival. The WINS study enrolled 2437 women who were within 1 year of diagnosis and randomized women to a low fat (15 % of daily intake) versus usual intake control group. After 5 years, the women in the low-fat dietary intervention group lost an average of 6 lb. There were significantly lower rates of recurrence in the intervention arm (HR, 0.76; 95 % CI, 0.60–98), especially among women with hormone receptor-negative disease (HR, 0.58; 95 % CI, 0.37–0.91) [129].

In contrast the WHEL study enrolled 3088 women who were up to 4-year post-diagnosis. Although the intervention group significantly increased their intake of fruits and vegetables and reduced their fat consumption, there were no significant differences in weight between the two groups. After a median follow-up of 7.3 years, there were no differences between groups in recurrence or survival [130]. However, upon further analysis, the combination of physical activity with diets high in fruits and vegetables did confer a survival benefit [131].

Other dietary interventions have yielded similar weight loss as the WINS trial in breast and prostate cancer patients (FRESH START) [132].

14.4.4.4 Diet and Exercise Interventions

A small study ($N=85$) used a cognitive-behavioral therapy approach of reduced energy intake and increased exercise to promote weight loss and risk for cardiovascular disease in breast cancer survivors and noted significant differences between the intervention and control groups after the 16-week intervention [133]. The intervention group demonstrated significant differences in weight, body mass index, percent fat, trunk fat, leg fat, and waist and hip circumference as well as reductions in triglycerides and total cholesterol and high-density-lipoprotein cholesterol.

A pilot study of postmenopausal breast cancer survivors ($N=14$) that was based on the Diabetes Prevention Program (DPP) demonstrated an average weight loss of 3.8 kg and a decrease in body mass index, percent body fat, and waist and hip circumference at 24 weeks with an additional weight loss of 0.8 kg at 36 weeks [134]. Although there were no differences in blood biomarkers at 24 and 36 weeks, the results of this pilot study demonstrate the efficacy of an intervention based on the DPP for early breast cancer survivors.

While there is a growing body of research demonstrating the efficacy of different approaches to weight management, there is a lack of rigorous prospective clinical

trials examining the effects of weight control and weight loss during and following cancer treatment in different types of cancers and on the end points of development or preventing comorbidities, recurrence, and improving survival. More research is needed to understand the optimal time for intervention, sequencing of interventional components (diet, exercise, behavioral change), and the impact of weight loss on health outcomes and health care costs.

14.4.5 Weight Loss After Treatment: Medical Management

14.4.5.1 Pharmacological Aids

Overweight and obesity increase risks for recurrence and comorbid conditions that may be mitigated with pharmacological, surgical, or integrative intervention [118]. Pharmacological management of weight loss is an option for individuals with a BMI of >30 or >27 kg/m^2 in persons with comorbid conditions. Pharmacological agents approved for weight loss are orlistat, lorcaserin, phentermine, benzphetamine, methamphetamine, dextroamphetamine, and phendimetrazine. Orlistat is the only drug approved for long-term use [135] and produces only modest weight loss (3 kg more than placebo) [136, 137]. Lorcaserin acts on the serotonin receptors to induce satiety. Other drugs in development combine phenteramine and topiramax, but safety in cancer survivors is unknown.

Anti-obesity drugs are not without side effects and must be used with caution, especially in cancer survivors who are already at elevated risk for cardiovascular problems. These drugs are usually prescribed when other weight loss approaches, such as diet, exercise, and lifestyle changes, have not been successful. The greatest weight loss is observed with pharmacotherapy when it is combined with exercise and lifestyle modifications [138, 139]. No clinical trials have been conducted of these weight loss drugs in cancer survivors. So, the safety profile is unknown, and it is unclear if the side effect profile will be similar or if other cancer-specific events may be noted in this population.

14.4.5.2 Botanicals and Natural Supplements

A variety of supplements are readily ingested by cancer survivors [140, 141], and although the Health, Eating, Activity, and Lifestyle (HEAL) study indicated red clover users were less likely to report weight gain among cancer survivors [142], no botanicals or supplements have demonstrated safety or efficacy in the prevention of weight gain or weight loss during or following cancer treatment.

Several botanicals have been tested in the setting of loss of appetite, nutritional deficiencies, and cachexia, but not prevention of weight gain or intentional weight loss among cancer survivors. Of popular interest, no formal research has been conducted on medical marijuana for weight gain. Anecdotal evidence would suggest that medical marijuana may not only ease many side effects of cancer and its treatment but also aid in appetite stimulation and weight gain among those suffering from loss of appetite, nutritional deficiencies, and cachexia.

14.4.6 Surgical Approaches to Weight Loss

Bariatric surgeries, including vertical banded gastroplasty, gastric bypass, and laparoscopic adjustable gastric banding, offer effective weight loss for severely obese persons with BMIs exceeding 40. Patients with BMI >35 and a weight-related health problem (diabetes, heart disease, or sleep apnea) and documented failure to lose weight in a medically supervised program (diet, exercise, counseling, or drug therapy) may be considered for bariatric surgery. While these procedures are effective for weight loss, they are generally not recommended for patients with a history of cancer within the past 5 years.

There is limited longitudinal data among obese women to suggest that weight loss reduces cancer incidence and mortality [143, 144]. This research highlights women because women generally seek bariatric surgery in higher numbers than men. While the reduction in cancer incidence and mortality is intriguing, these studies have been based on a small number of morbidly obese patients, very few of whom had cancer and none of whom were receiving active treatment [138, 145]. The notion that bariatric surgery reduces mortality has not yet been confirmed but does raise intriguing questions about the relationship of weight loss and cancer survival [146]. Bariatric surgery is not without risks and should be balanced against the possible benefits.

14.5 Future Directions

In general, the field of weight management in survivorship is early in development. It is important to note again that the amount of evidence across cancer types is not equal. Weight management interventions among breast cancer survivors dominate the literature, while other cancers are less well studied. The limited evidence for weight management strategies in some cancers should not be over-interpreted. Study results may not have been null or negative, but rather, research in certain cancers has not been well funded or sufficiently studied to date. Therefore, the most obvious future direction for weight management research in cancer survivorship is to expand trial diversity in a number of ways, including cancer types, intervention types, racial/ethnic diversity, age, and geographic location. Fortunately, several promising studies are ongoing in other cancer types and in more diverse populations. The recent call for high-quality exercise trials among prostate cancer survivors receiving androgen deprivation therapy [147] has the potential to spark further investigations in prostate cancer and other cancer types.

Since smoking cessation is recommended to improve outcomes and reduce the risk of recurrence and second cancers in all cancer survivor populations, weight management support in survivor smoking cessation programs may also be needed. One study noted that smoking-associated weight gain in breast cancer survivorship was primarily attributable to quitting smoking [31]. Interventions for preventing weight gain after smoking cessation in the general population may be adapted to be clinically appropriate by cancer type [148].

Another important contribution to the field of weight management in cancer survivorship would be a better understanding of the optimal time for intervention, sequencing of interventional components (diet, exercise, behavioral change), and the impact of weight loss on health care costs as well as health outcomes. Further data on the safety and efficacy of supplements, weight loss medications, and surgical interventions among survivors is nearly absent.

If we are to make progress, it must be noted that adequate funding to power randomized controlled trials and follow participants long term is critical to understanding lifestyle and weight management influences on morbidity and mortality. There is not enough evidence to determine if weight loss or prevention of weight gain among cancer survivors is truly beneficial for these long-term outcomes.

In spite of the limitations in our research knowledge base, some suggest that it is appropriate for physicians to counsel their patients to lose weight following obesity-related cancer diagnoses, emphasizing the benefits of healthy diet and physical activity beyond, but potentially including, improving long-term outcomes. For now, caution should be used when considering translating weight management strategies, particularly for weight loss, between cancer types and treatment types because the etiology of weight gain and the risks involved with specific weight gain prevention and weight reduction strategies may vary across cancers types and cancer treatments. Thus, it is prudent to adhere to evidence-based medicine by cancer and treatment type. However, for most cancer survivors, physical activity is considered to be safe and to positively alter body composition, if not body weight [119]. Ongoing and new trials of lifestyle and medical interventions will provide further evidence for or against prevention of weight gain and weight loss in survivorship.

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Genetic Counseling and Risk Assessment 15

Joanne M. Jeter

Since the early 2000s, improved understanding of the molecular biology of disease has led to the "era of personalized medicine." Personalized medicine refers to the use of genetic, genomic, and other individual characteristics and exposures to define disease in an individual and to influence treatment and management decisions. With the wealth of genetic information now available, significant advances have been made in the prevention and treatment of many types of cancer, and the interpretation and communication of this information are an important clinical need.

However, the concepts of risk assessment and genetic counseling date back significantly further. In 1975, a subcommittee of the American Society of Human Genetics published a statement defining genetic counseling as "a communication process which deals with the human problems associated with the occurrence, or risk of occurrence, of a genetic disorder in a family" [1]. In this seminal paper, the authors delineate the following goals for genetic counseling:

1. Comprehension of the medical facts of the diagnosis, natural history, and management options for the disorder
2. Appreciation of the hereditary contribution of the disorder and the associated risk in relatives
3. Understanding of the options for treatment of the disorder
4. Selection and implementation of an appropriate management plan with attention to risk, family situation, personal ethics, and religion
5. Facilitation of the adjustment to the disorder in the patient and the family members

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More recently, the National Society of Genetic Counselors proposed their own definition, which emphasizes the integration of assessment of family and medical histories to determine the chance of the disorder; education about the inheritance, testing, management, prevention, resources, and research; and counseling to inform choices and adaptation to the disorder [2]. Central tenets of genetic counseling include voluntary participation, informed decision making, protection of privacy, and consideration of the psychosocial aspects of testing and its outcomes.

15.1 Criteria for Referral for Genetic Counseling and Testing

Professional organizations, both in genetics and in oncology, endorse the use of genetic counseling in order to provide appropriate education and allow for informed consent prior to performing genetic testing [3–9]. Criteria for referral for genetic counseling have been published in the medical literature [10, 11]. Other sources, such as the National Comprehensive Cancer Network, have also established their own guidelines, which are frequently used by insurance companies as well as by clinicians to determine coverage.

General hallmarks for inherited cancer syndromes include cancers diagnosed at an earlier age than would normally be expected, multiple separate primary cancers in the same individual (and/or bilateral cancers in paired organs), patterns of specific cancers on one side of the family, and the occurrence of rare cancers, such as male breast cancer or pheochromocytoma, known to have a strong hereditary genetic component. In addition, ethnic background may play a role for groups known to have a founder mutation predisposing to cancer. The primary example of this situation is the increased incidence of *BRCA1* and *BRCA2* mutations in the Ashkenazi Jewish population.

Similarly, criteria for the ordering of genetic testing have also been described by professional organizations. The American Society of Clinical Oncology (ASCO) recommends that genetic testing may be performed if an individual's personal or family history is suspicious for a genetic predisposition to cancer, the test has sufficient sensitivity and specificity for interpretation, and the test will impact the management of cancer or cancer risk in the individual or will help clarify risk in family members [3, 4].

15.2 Prerequisites for Counseling

Genetic and risk assessment counseling encompasses multiple disciplines. Although the genetic counseling session itself is usually done by a genetic counselor, a multidisciplinary team approach may be taken, with input from medical geneticists, genetics nurse practitioners, oncologists, surgeons, gynecologists, other medical subspecialists such as gastroenterologists, and psychiatrists or psychologists.

Several studies have demonstrated the need for subspecialized training in cancer genetics in order to perform genetic testing knowledgably. Wideroff et al. showed

that deficits were present in knowledge of common hereditary cancer syndromes in a population of general practitioners and subspecialist physicians [12]. Another survey of medical practitioners revealed that understanding of risk-appropriate management strategies and provision of genetic counseling services was lacking [13]. Other studies have indicated a need for further education regarding documentation and use of family cancer history, as well as legal protections against genetic discrimination [14–18].

Table 15.1 National Coalition for Health Professional Education in Genetics: core competencies

Knowledge
1. Understand basic human genetics terminology
2. Understand the basic patterns of biological inheritance and variation, both within families and within populations
3. Understand how identification of disease-associated genetic variations facilitates development of prevention, diagnosis, and treatment options
4. Understand the importance of family history (minimum three generations) in assessing predisposition to disease
5. Understand the interaction of genetic, environmental, and behavioral factors in predisposition to disease, onset of disease, response to treatment, and maintenance of health
6. Understand the difference between clinical diagnosis of disease and identification of genetic predisposition to disease (genetic variation is not strictly correlated with disease manifestation)
7. Understand the various factors that influence the client's ability to use genetic information and services; for example, ethnicity, culture, related health beliefs, ability to pay, and health literacy
8. Understand the potential physical and/or psychosocial benefits, limitations, and risks of genetic information for individuals, family members, and communities
9. Understand the resources available to assist clients seeking genetic information or services, including the types of genetic professionals available and their diverse responsibilities
10. Understand the ethical, legal, and social issues related to genetic testing and recording of genetic information (e.g., privacy, the potential for genetic discrimination in health insurance and employment)
11. Understand one's professional role in the referral to or provision of genetics services and in follow-up for those services
Skills
1. Gather genetic family history information, including at minimum a three-generation history
2. Identify and refer clients who might benefit from genetic services or from consultation with other professionals for management of issues related to a genetic diagnosis
3. Explain effectively the reasons for and benefits of genetic services
4. Use information technology to obtain credible, current information about genetics
5. Assure that the informed-consent process for genetic testing includes appropriate information about the potential risks, benefits, and limitations of the test in question
Attitudes
1. Appreciate the sensitivity of genetic information and the need for privacy and confidentiality
2. Seek coordination and collaboration with an interdisciplinary team of health professionals

Core competencies have been published by the National Coalition for Health Professional Education in Genetics (Table 15.1). In addition, ASCO has established necessary criteria for a genetic counseling session. For the pretesting sessions, the following items are considered the basic elements required for consent:

- Information on the specific test being performed
- Implications of a positive and negative result
- The possibility that the test will not be informative
- Options for risk estimation without genetic testing
- The risk of passing a mutation to children
- Technical accuracy of the test
- Fees involved in testing and counseling
- Psychological implications of tests results (benefits and risks)
- Risks of insurance or employer discrimination
- Confidentiality issues
- Options and limitations of medical surveillance and strategies for prevention following testing
- Importance of sharing genetic test results with at-risk relatives so that they may benefit from this information [4]

In the 2010 update to this policy statement, Robson et al. recommended that information on whether the counselor was employed by the provider of the test should be added for direct-to-consumer testing [3]. Other additions in this update included information on whether the range of risk associated with the variant being tested will impact medical care, licensure of the lab (when appropriate), possible use of DNA testing samples in future research, and plans for follow-up after testing.

Posttest counseling sessions should focus on interpretation of the test results, discussion of any further testing that may be recommended, assessment of the patient's response to the results, recommendations for communication of the results to family members, and recommendations for cancer risk management. For individuals with negative or uninformative results, they are reminded of the potential for discovery of new genetic causes in the future that may be relevant to the risk for themselves or their families.

15.3 Risk Assessment

Assessment of cancer risk often starts with a psychosocial assessment to determine the patient's concerns and expectations. The patient's prior experiences with cancer, preexisting psychological conditions, support system, and cultural or religious background may all play a role in their need for evaluation of cancer risk. Because the genetic evaluation process involves discussion of family members who may have had cancer, may be deceased, or may be otherwise estranged from the patient, the person providing the counseling should determine if uncontrolled depression or

anxiety is present prior to testing. On occasion, genetic testing or counseling may need to be deferred until the psychiatric issues are addressed.

Clinical information to be obtained for risk evaluation includes age, race/ethnicity, personal history of cancer, exposure history, reproductive history, diet and exercise practices, and date and outcome of last cancer screening examinations. For patients with cancer, the age at which they were diagnosed, the type of cancer and its pathology, the treatment(s) of the cancer, and the current surveillance plan are all relevant. Physical examination findings such as increased head circumference for individuals being evaluated for Cowden syndrome or cutaneous findings for genodermatoses associated with hereditary cancer syndromes may play a role. Some practitioners also perform breast or gynecologic examinations if these are appropriate for the cancer risks of concern.

Documentation of the family history is performed through constructing a pedigree. This information may be obtained from responses from questionnaires, patient interviews, or both. This format provides a visual representation of the patterns of disease occurrence in terms of the familial relationships. The pedigree should consist of all first- and second-degree relatives on both sides of the family, giving information on at least three generations. Race and ethnicity of the grandparents should be noted in order to determine if specific founder mutations may be present. Adoptions and nonpaternity should also be recorded, and the information should focus on the histories of the biologic family members. For family members with cancer, the site of cancer, age of diagnosis, history of risk-reducing treatments and/or treatments for the cancer, current age or age at death, exposures, and current residence are all important information, as well as their history of genetic testing and results if known. Ideally, cancer diagnoses for family members affected with cancer can be confirmed by pathology reports; however, in practice, this information may be difficult to obtain. The results for genetic testing of family members can also be critical components of the evaluation, and reports from these tests should also be obtained when possible, even if they are negative. With changes in the availability and scope of genetic testing, a result that was negative in the past may be considered incomplete today, due to availability for testing beyond full sequencing to include deletion/duplication analysis.

Studies of the accuracy of family histories obtained from the patient have had varied results. One study showed that only 6 % of people did not know if a first-degree relative had cancer, and 8.5 % did not know if a second-degree relative had this diagnosis [19]. Other studies have confirmed that reporting is more accurate for close family members and that a report of no cancer tends to be more reliable than a report of cancer [20]. Some types of cancer appeared to be more likely to be described correctly: reports of breast cancer tended to be more accurate than those of gynecologic or colon cancers [20, 21]. Additional factors that may affect the accuracy of reported family histories are estrangement from family members, deceased family members, limited family structure, or lack of individuals of the gender characteristically expressing the inherited conditions. Lastly, the family history may change over time, and so patients should be reminded to notify the

counselor of any new diagnoses, particularly if their genetic testing results are negative or uninformative.

The pedigree information can allow for the determination of any inheritance patterns that may be apparent for the history of cancer. Most inherited cancer syndromes show autosomal dominant inheritance patterns, but some exceptions exist, such as autosomal recessive inheritance for *MUTYH*-associated polyposis and ataxia-telangiectasia. However, most cancers are due to complex or multifactorial disease inheritance involving polymorphisms of multiple genes or the interactions between genes and environmental factors. Single-gene mendelian disorders are rare and account for a fairly small percentage (5–10 %) of cancers but have a high relative risk compared to that of the general population; genetic polymorphisms, on the other hand, occur frequently in the population but have a low relative risk of cancer.

With the personal and family history information, risk models can be applied to determine the risk of harboring a deleterious mutation or the risk of cancer. Multiple models to assess risk exist; however, care must be taken to apply the correct model to the patient. Some account only for first-degree relatives with cancer or only apply to individuals over a certain age. For assessment of risk of a genetic mutation, some models determine the risk for the family, and others assess the risk for the individual. Most models are based on studies of a predominantly Caucasian population, as well, and considerable uncertainty is present for applying these models to individuals of other races. The most definitive means of assessing cancer risk is through determining the presence of an inherited cancer syndrome by identifying a genetic mutation; therefore, genetic evaluation trumps any other risk factors that may be described. At this time, there is no reliable model that accounts for all relevant risk factors for an absolute cancer risk estimate.

15.4 Genetic Testing

Evaluation of the pedigree can allow for determination of the most appropriate person for genetic testing in the family. This individual ideally would be the person most representative of the syndrome being evaluated, either due to having cancer diagnosed at the earliest age, multiple cancers in the same individual, bilateral disease, or other associated characteristics of the syndrome. Unfortunately, due to the nature of these disorders, the individual most appropriate for testing may be deceased. If a mutation has been identified in the family, documentation of the specific mutation should be obtained to facilitate appropriate testing. If no one affected with cancer is living or available for testing, testing may be considered for unaffected family members at risk; however, these individuals should be counseled regarding the potential for uninformative results when a mutation has not been identified in the individuals with cancer in the family. In this instance, a negative result would be considered uninformative, as the cause of the cancers in the family has not been identified. Patients should also be counseled regarding the possibility of identification of a variant of uncertain significance, or a change in the genetic sequence for which there is insufficient data to determine if it is associated with an increase

in cancer risk. Depending on the frequency at which these variants occur in the population, reclassification of these variants may take years. Evaluation of the variants on a molecular, clinical, and evolutionary level may help in reclassification, but in the absence of these data, clinical decisions are often made on the basis of the family history.

Genetic testing in the prenatal setting requires special consideration. Some of the issues that must be assessed include the probability of childhood malignancies, morbidity, and mortality; the penetrance of the mutation; the severity of the associated phenotype; and the availability of interventions to decrease cancer risk or to detect the associated cancers at a treatable stage [3, 4]. For most inherited cancer syndromes that manifest in adulthood, prenatal testing or testing in childhood is not encouraged, as it is unlikely to impact clinical management in the first decades of life [22–24].

15.5 Multiplex Genomic Testing

Test panels assessing for mutations in multiple genes simultaneously have become available on a commercial basis. These tests, conducted via next-generation sequencing, often have costs comparable to those of single-gene testing but may contain assessment for lower-penetrance mutations. The benefit from using these panels is the potential identification of deleterious mutations that are not suggested by the family or personal history; however, the management of individuals with deleterious mutations and no family history consistent with the disorder remains unclear at this time. Potential hazards of use of these multigene panels include the high rate of variants of uncertain significance and the lack of management recommendations for the lower-penetrance genes.

Although original guidelines for genetic testing were designed to assess for single-gene Mendelian disorders, more recent guidelines have been updated to account for low- to moderate-penetrance genes, as well as the direct-to-consumer marketing of genetic and genomic testing. ASCO's policy statement from 2010 recommends consideration of the clinical utility of a test, regardless of whether it is obtained through a healthcare professional or direct to consumer. At present, the utility of low- and moderate-penetrance genes, such as *CHEK2*, remains uncertain [3]. If tests of unclear clinical utility are ordered by the patient or by a practitioner, follow-up counseling should include discussion of the lack of evidence regarding the use of such testing. In these situations, screening and other cancer risk management should be based on established risk factors.

15.6 Protection Against Genetic Discrimination

Patients considering genetic testing often express concerns about the potential for insurance or employment discrimination on the basis of their results. In 2008, the United States Congress passed the Genetic Information Nondiscrimination Act,

which provides protections for employment and health insurance for those with genetic conditions. It is important to note, however, that this legislation does not apply to life insurance or disability insurance for these individuals [25].

Conclusion

Overall, more than 200 hereditary cancer syndromes have been described in the literature, and the areas of genetics and genomics hold immense potential for cancer prevention and therapeutics. With the assistance of individuals trained in the appropriate use and interpretation of these genetic tests, the promise of this science can become a reality that benefits our patients and their families.

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Cancer Survivorship in the Digital Age

16

Ana Maria Lopez

16.1 The Problem

The diagnosis of cancer has surpassed heart disease as the greatest cause of morbidity and mortality for certain age groups in the USA [1]. Once a diagnosis is inextricably linked to mortality, this array of illnesses falling under the umbrella of cancer is now increasingly associated with survival [2]. The number of cancer survivors in the USA is growing [3]. The two most prevalent cancer diagnoses found in this blend of survivorship, outside of nonmelanoma skin cancer, are persons with a history of breast or prostate cancer [4]. Improvements in survivorship have been achieved for most malignancies afflicting children or adults. Some of these improvements have been, albeit, modest [5].

16.2 Evidence

The recognition of cancer's impact beyond the acute disease, its diagnosis and treatment, and beyond the individual patient has been unequivocally documented in the literature. Optimizing survivorship has emerged relatively recently as an area of interest for the medical community [6]. Having been championed by patients and their families for decades, these efforts may be seen as a harbinger for the growing emphasis on patient voice as a measure of quality and a critical component in improving health outcomes.

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16.3 Ongoing Research

The rapid rise of information technology has been unparalleled [7]. Once thought to be the domain of Star Trek, there is a current competition to develop the famous Tricorder, a portable, wireless device that fits in the palm of your hand and can diagnose and monitor a host of health conditions, all as if with the wave of a wand [8]. Telemedicine, telehealth, e-medicine, and digital medicine are all variants on a common theme—using of telecommunications technology to address healthcare needs [9]. The variety of approaches is staggering. In this chapter, I will define and discuss telehealth interventions that have been documented to make a difference in cancer survivorship, outline possible future interventions, and discuss evaluation modalities.

Cancer survivorship begins at the time of diagnosis [10]. Cancer impacts the patient, the survivor, and her/his family, friends, and community—also known as the co-survivors [11]. Addressing the critical concerns of the survivor and the co-survivor requires interventions that target the survivor/co-survivor, the healthcare team, and the healthcare system within which the survivor receives care. Telehealth approaches can impact each of these critical domains.

Factors of concern to the survivor and co-survivor are:

- Demystification of the disease process—what may I expect? Is this normal?
- Access to successful low-cost, low-side-effect interventions that can prevent and/or address long- and short-term treatment side effects—what can be done to help me feel better?
- Prescription of evidence-based cancer prevention, primary and secondary—screening, measures—what can I do to prevent this cancer or any other cancer from entering my life in the future?

Healthcare professionals require support in order to:

- Stay current on high-value survivorship care—what works? What do I recommend?
- Care for survivors in underserved communities
- Engage survivors/co-survivors toward cancer clinical trials

The healthcare system is increasingly strained and requires support to:

- Implement health system changes to deliver optimum care—how do I integrate these recommendations into my “7-min” visit? How do I help my patient navigate the morass of options and the obstacles of the healthcare system?
- Provide on-demand care and education
- Meet the multicultural needs of our increasingly diverse population

16.4 Solutions

From our work with long-term cancer survivors, women with a history of breast cancer for 5 years or more living in urban and rural settings, the ongoing side effects of depression, anxiety, and fatigue were prevalent. Survivors' number one request to address these needs was knowledge. They sought educational interventions to ameliorate their fear which was seen as the root of their symptoms [12].

Demystification of the disease process that addresses expectations and the wide range of new normal possibilities provide survivors with a better understanding of the landscape that they are now facing [13]. Much of what is accomplished in the clinical encounter is education. Increasing time pressure along with considerations of the principles of adult learning may induce us to look more closely at group models of both education and care [14]. Utilizing telemedicine technologies to facilitate access to education can improve access to the "remedy" while bridging to at-need populations that would otherwise remain under the radar screen and underserved.

Telehealth interventions may also be utilized to provide direct care [15]. Survivors seek successful low-cost, low-side-effect interventions that can prevent and/or address long- and short-term treatment side effects. Survivors want to feel better. Although a compendium of long- and short-term side effects with therapeutic interventions is beyond the scope of this work, an example may provide a helpful illustration.

Mrs. J is a 42-year-old woman, single mother of two children ages 10 and 6, and she also teaches 4th grade. She is living in a community approximately 90 min from the cancer treatment center and is a survivor of stage II breast cancer that was incidentally discovered when she sought care for a bilateral tubal ligation. She successfully completed surgery, chemotherapy, and radiation and found herself ready to face the "rest of her life left to wonder when the other shoe would drop." She had "survived" chemo by eating comfort food and gaining nearly 30 lb. No one had spoken with her with concern about the increase in weight during treatment. Mrs. J thought the weight gain was an inevitable result of her premature menopause due to the chemotherapy and that she'd quickly lose it like she'd lost her "baby fat" when she heard her oncologist's remark that "losing the weight would be a good idea" at her last oncology visit. Her follow-up had been primarily relegated to her primary care physician whom she had not met yet as her health plan had just assigned her a new primary care physician. She generally had seen her primary care physician only intermittently as she had seen herself as healthy and she did not wish to accrue any "unnecessary" healthcare costs.

After the first posttreatment visit, she began to relook at herself and found that she was "cancer-free" but not symptom-free, not healthy. She noted joint pain, decreased mobility and balance, prediabetes, elevated cholesterol, and sleep apnea. In addition, she related being very upset to now understand that since she is so young, her breast cancer may be hereditary and she may have "contaminated" her children. She does not wish to return to the cancer care center because it reminds her of being ill; furthermore, the round-trip travel of about 3 h is difficult to manage alongside the demands of her family and her work.

Telemedicine interventions may help address many of these concerns. Home monitoring units may be utilized to help her address many of her clinical concerns. A home sleep study can be conducted and has the potential for improved accuracy due to recording sleep in the patient's own familiar setting [16]. Although the patient has some awareness that weight loss means modulating her oral intake and increasing her physical activity, she does not have the ready knowledge and/or tools to help her meet her goals. Providing the patient with a home health telemedicine unit will allow her to connect to her virtual healthcare team for telenutrition education [17], telemovement group sessions [18], and telediabetes prevention [19] visits. These programs can be conducted as individual point-to-point sessions but have the potential for nurturing virtual communities that serve to learn and experience changed behavior together. The electronic connection at her primary care doctor's office may be used for direct provision of services such as telegenetics, telebehavioral health, and ongoing survivorship follow-up and high-risk management to include evidence-based cancer prevention, such as primary and secondary screening, which may include mobile technology reminders and support [20]. These high-tech and high-touch tools can support the patient's path to health through improved mental health, discovery of breast cancer hereditary risk, weight loss, improved mobility and balance, decreased fasting glucose, decreased lipids, and resolution of sleep apnea.

Integration of telemedicine technologies as described above into cancer survivorship care has not been fully implemented and actualized. The pieces are present; however, full integration remains a vision for the future.

Home monitoring technologies are increasingly available and hold great promise. Tools from glucometers, to pulse oxygen monitors, to home sleep studies are increasingly commercially available. Integration into the electronic health record to facilitate access of data to the patient's healthcare team is variable. Monitoring tools require FDA approval if used as clinical data that the patient shares with her/his clinical team. Use of these tools may require calibration and reliability assessments as a clinical tool.

Data regarding teleconsultations are available in some settings. Generally, teleconsultations may be conducted in real time, that is, as fully interactive videoconferenced consultations that may include attachments that enable a full physical exam, with the exception of palpation, to be conducted or as store-forward sessions that are generally focused clinical questions that are utilizing a digital photo or image to be interpreted, e.g., teledermatology or teleophthalmology: virtual retinal screenings. Our group has experience in telegenetics consultations which are conducted as real-time sessions and allow the patient to access cancer genetics counseling at a distance. This successful real-time application bridges geographic distance, decreases child and/or elder-care costs, decreases loss of wages due to work absence, and improves clinical efficiencies and access to care [21].

Telebehavioral health has a long history of success as a telemedicine application. Models utilizing mid-level providers or psychiatrist for medical management have all demonstrated clinical care improvements. Being primarily a "talk is therapy" telemedicine application, telebehavioral health has been more easily translated into the virtual setting by means of high-fidelity digital videoconferencing technologies.

Whereas the patient and the behavioral health specialist can typically sit in the same room facing each other to address the patient's needs, the patient and telebehavioral health specialist can similarly sit facing each other to address the patient's needs by virtue of the presence of a camera and a plasma screen [22].

Telemammography has been successfully conducted by our group with turnaround times that changed the clinical environment. Women no longer arrived alone for breast screening and left wondering what the results might be. Instead, women came as a group for breast screening, left for coffee or lunch, and returned to obtain the results. These women were no longer lost to follow-up [23].

Our experience with group delivery of care has been gained in telenutrition, telediabetes prevention, and telemovement. The use of telemedicine technology lends itself well to group formats. Care must be taken in the location of the microphones to assure that all voices are adequately heard. Optimally, cameras will be managed by a technical coordinator, not by the learners—survivors and co-survivors, who can focus on the speaker to mimic direct in-person communication. As in any group setting, the clinician-educator must skillfully facilitate the conversation to assure engagement, investment, and commitment to self-care. Interactivity is critical to the success of the educational intervention. Questions may be answered via direct interactive videoconferencing technology, webinar format, e-mail interaction, and chat room-like communication [24].

Mobile technology and apps in cancer care are increasingly available. These simple technologies may prove transformational in cancer care. With nearly universal use of cell phone technologies and growing use of smart phone and other mobile technologies even among underserved populations, these efforts hold much promise. Initially, emerging as texts to support tobacco cessation, screening behaviors, and weight loss support, new apps entering the market may provide tailored interventions to support cancer survivorship recommendations [25].

Development of patient portals integrated into the EHR for symptom management may be especially effective for survivors and co-survivors to report symptoms and receive on-demand intervention recommendations in real time. Our experience in portal development for symptom management has utilized a nurse-based as well as evidence-based decision-support system that can be accessed by the patient for assistance in symptom management. This phone or computer-based system allows the patient to experience a more timely relief of symptoms. Our work has developed complementary cancer-specific social media sites where the patient is able to interact with her/his support system, her/his clinical team, the symptom-reporting portal, and chat room and virtual clinical education resources all through a single website. This system supports patient-centered care and preserves patient autonomy during a vulnerable time when patients and families explicitly note a feeling of loss of control [26].

The medical landscape is increasingly turbulent and difficult to navigate. Cancer care navigators exist in various settings, yet the role of the cancer navigator is not uniform across all settings. In Arizona, community health workers and/or *promotoras* serve to facilitate access to care, including cancer care, to patients in underserved communities. Often respected community leaders who have gained knowledge regarding cancer care, community health workers, and/or *promotoras* may not have

formal cancer education or be up to date on electronic health information resources, technologies, or programs. Our group has successfully implemented a virtual synchronous and asynchronous course for community health workers and/or *promotoras* in cancer care and electronic health information resources, technologies, or programs that graduate *e-* community health workers and/or *promotoras*. Starting the course with minimal computer literacy, *e*-community health workers and/or *promotoras* end the course actively utilizing e-mail, connecting to each other via social media, and having developed a patient education resource (through Microsoft Word, Excel, and/or Publisher) for use with their patient population. The *e*-community health workers and/or *promotoras* have access to online community resources and networks to better serve their patient population better [27].

16.4.1 Healthcare Professionals

Healthcare professionals face an ever-growing challenge in the digital age: how to keep up with the increasing demands of their practice. This challenge is greatest for the generalist who is increasingly expected to meet a diverse group of standards and metrics in an even shorter amount of time. CME is often received in a Grand Rounds format, such as an interactive lecture. Considering the general level of fatigue found among physicians, tailored and targeted active learning modalities may be more fruitful.

Telehealth educational solutions can consider the needs and interests of the communities to be served to develop targeted programming that engages learners in their area of interest. The Arizona Telemedicine Program (ATP) at the University of Arizona assesses the needs of its community of learners on an annual basis. This annual survey serves as the foundation for the ATP Grand Rounds, Nursing Grand Rounds, and our partner interprofessional and patient education series called "*¡Vida!* " [28]. Existing technologies allow access to education on-demand and on different platforms. Current efforts are in place to search and access specific content.

A chart rounds is a novel-distributed educational intervention that gathers learners from a single site or from multiple sites, who have clinical questions within a specific discipline, i.e., diabetes or adolescent medicine. Participants virtually gather together their clinical questions and review the case-based question with a clinical expert in the discipline being addressed. Utilizing the principles of adult learning, learners receive content in a relevant manner, through a clinical scenario and gain the benefit of multiple clinical scenarios in the hour-long session.

Tumor boards allow for a multidisciplinary review of the cancer patient's disease status. They may be coordinated as virtual tumor boards by combining together multiple telemedicine applications, i.e., teleradiology, telepathology, telemedical oncology, telesurgical oncology, and teleradiation oncology with telesupportive and palliative care and telesocial work as needed [29]. By means of fully interactive videoconferencing, clinical participants and their patients—at a distance—can gain benefit from the insights of the telemedicine consultants.

All efforts can be supported by webinars, which are developed of virtual learning communities that engage via e-mail, chat room-like, and Twitter discussions.

16.4.2 Healthcare System

The healthcare system is increasingly strained and requires support to improve integrated care. Lack of healthcare integration results in medical errors, more costly redundant care, and hospital readmissions [30]. Home health technologies range from videophones, smartphones, tablets, or tabletop units that include attachments to conduct portions of the physical exam and/or for self-monitoring. These may be used to support adherence to treatment recommendations, monitor the real-time response to clinical interventions, and adjust treatment recommendations based on clinical data earlier in the treatment process. These timely interventions contribute to the delivery of optimum care [31].

Although most practices have been integrated into the electronic health record, patient tools for patient education, shared decision-making as well as clinical tools for decision support and access to the medical literature are not ubiquitous. The former may help the survivor and co-survivor to navigate the morass of options and the obstacles of the healthcare system. The latter assists the clinician in the provision of evidence-based and high-value clinical care.

Access to cancer clinical trials and enrollment in cancer clinical trials from prevention to palliation is poor in nearly all clinical settings. With many survivors living in rural America or in underserved urban settings often greater than an hour travel time to a cancer center, use of telecommunications technology can improve access to appropriate trials and engage survivors/co-survivors in cancer clinical trials. Through fully interactive high-definition technology, the ATP Network has, for example, connected a cancer patient at a member site with a research team member at the University of Arizona Cancer Center (UACC) for assessment of entry into a cancer clinical trial. If eligible and interested, the patient can be consented through this virtual interaction, and study orders can be placed in preparation for the in-person visit, study entry, and participation. This innovative use of the ATP Network may facilitate clinical trial entry for underserved populations [32]. Access to telecommunications technology allows for complementary support with on-demand care and education.

Facing the evolving needs of an increasingly diverse patient population with multiple language needs and healthcare belief systems can cause difficulties to the health system. Telehealth innovations that utilize virtual medical interpreters can help to ameliorate these needs. Whether a spoken language or American Sign Language, clinical data demonstrates the success of these virtual interventions [33].

16.5 Future Directions

This review demonstrates both the possibilities for telehealth interventions in cancer survivorship as well as the lack of integration of telehealth services in cancer survivorship care. The rapid development and entry of these technologies into the healthcare market has made access to these tools easier. New self-monitoring tools and health apps are emerging daily. How best to integrate these tools remains to be discerned. Future work will likely include development and assessment of *e*-Survivorship

Toolkits that may incorporate access to patient education, online risk recurrence tools, symptom-reporting portals, social media, the electronic health record's patient portal, local or regional cancer clinical trial searches, finance apps, local electronic searchable disease-specific resource guides, and tailored and interactive survivorship plans.

Healthcare professionals may increasingly utilize telehealth interventions to provide care to survivors in underserved communities. Clinical work in some settings integrates decision support, i.e., in mammography, computer decision aids. Increased integration of searchable professional education resources, decision-support aids, patient reminders, and evidence-based data into the electronic health record has the potential to improve care with on-demand support for tailored patient care. Use of these technologies on multiple platforms and with opportunities to model integrated care to students and trainees will allow clinical learners to become proficient in virtual care.

The healthcare system is strained. Cancer survivors and co-survivors require specific care and support to maintain health. Telehealth technologies can help extend healthcare resources beyond the hospital or clinical center's walls to deliver care where it is needed and when it is needed. This ability to tailor access to healthcare resources in an integrated manner has the potential to improve clinical efficiency and decrease healthcare costs due to timelier care, cancer prevention, and greater follow-through on cancer screening recommendations.

Although the focus of this chapter has been on cancer survivorship in the USA, we must note that cancer is no longer a class of diagnoses that is seen with rarity outside of developed countries. Cancer has gone global. Countries once considered "low risk" for cancer are now actively preparing for the care of the high numbers of cancer patients and planning ahead for the anticipated increases in cancer incidence and, hopefully, in cancer survivors. These realities emphasize the need for improved understanding of cancer survivorship and for innovative and sustainable models of care that can target survivor needs across the spectrum of cancer care. With the profound proliferation of telecommunications technology, low-cost interventions that utilize smartphones or tablets have untapped potential in low resource communities nationally and internationally.

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Health Economic and Outcomes Research in Cancer

17

Grant H. Skrepnek

17.1 Value Determinations in the Existing System of Cancer Care

A substantial clinical and economic burden of illness is extolled upon persons across the spectrum of cancer, also impacting the welfare of society overall [1, 2]. This burden persists despite marked improvements in survival rates in recent decades. Despite recent advances to improve prevention, detection, and treatment with approximately 1,000 investigational drugs in development, tremendous barriers continue to persist in cancer that ultimately impede optimal care for patients [3, 4]. Achieving a cancer care system that is effective, efficient, and equitable remains both a priority and a challenge among providers and policy makers. While various definitions of quality and value exist, both cost and access remain of central concern. Through comprehensive health technology assessments or pharmacoeconomic analysis, empirical evidence seeks to maximize patient-centered outcomes for each resource expended across the continuum of cancer, also providing a formal and robust approach to directly incorporate patient preferences. The careful balance between infinite wants and finite resources warrants continued empirical evidence to guide healthcare systems toward optimal effectiveness, efficiency, and equity.

- Articulate goals consistent with this vision of quality cancer care;
- Implement policies to achieve these goals;
- Identify barriers to the practice and receipt of quality care and target interventions to overcome these barriers;
- Further efforts to coordinate the currently diverse systems of care;
- Ensure appropriate training for cancer care providers;

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- Have mechanisms in place to facilitate the translation of research to clinical practice;
- Monitor and ensure the quality of care; and
- Conduct research necessary to further the understanding of effective cancer care. [4]

More recently, the American Society of Clinical Oncology (ASCO) report on "The State of Cancer Care in America, 2014" emphasized the increased importance of quality measurement and value demonstration, identifying three principal factors to be considered when continuing to improve cancer care in that: (1) demand continues to increase for services relating to cancer prevention, screening, and treatment; (2) access to care remains fragmented and disproportionate; and (3) an urgent need is required to improve the value of care [2]. The main system-wide issues to be considered in developing a model of cancer care revolve both within and between five stages of interventions: (1) prevention; (2) screening; (3) treatment; (4) continuing care and risk management; and (5) palliative care [5].

Defining and optimizing cancer care and any accompanying health policy to achieve this remains complex and challenging, issues that become especially important concerning cancer control and prevention, supportive care, and survivorship. Concerns of treatment disparities, under- or overutilization, comparative effectiveness, and cost-effectiveness have become increasingly critical. Research involving outcomes, comparative effectiveness, and health technology assessment or pharmacoeconomics offer robust frameworks to provide relevant information for clinicians, patients, payers, and other key decision makers to maximize patient outcomes at, ultimately, the lowest cost. Importantly, consensus has emerged that advocates for a more comprehensive and comparative evaluation of various medical interventions to support effective, efficient, and equitable use among patients and across populations [6]. Developing health recommendations to prevent, treat, and cure cancer often involve potential trade-offs that must be empirically quantified, yet consider ethical elements that might extend beyond a study's immediate calculus. Although medical advances have resulted in greatly improved life spans, questions have emerged if the corresponding costs associated with these innovations have been exceedingly offset by their benefits to improve the welfare of society as a whole [7–9].

Given that expenditures associated with cancer are increasing at a rate substantially higher than both total healthcare spending overall and markedly faster than the gross domestic product, cost and value considerations have emerged among patients, payers, and providers [7, 8]. Although the sources of oncology-related costs are multifaceted, increases in expenditures have specifically been attributed to more expensive treatments with varying degrees of real-world effectiveness, increased treatment intensity associated with more aggressive protocols, and longer treatment time periods that are reflective of increased survival rates [7].

Ramsey (2009) commented that several characteristics inherently specific to cancer may have ultimately discouraged the study of safety, effectiveness, and cost-effectiveness associated with interventions [7]. Given the often life-threatening nature of the disease, for example, an urgency to adopt new medical treatments with less certain

outcomes than usual care may be based principally on perceptions of need versus that of known evidence of effectiveness or safety. Difficulties in communicating cost and value during clinical encounters may also be present, even potentially viewed as unimportant, inappropriate, or offensive [7]. Distress surrounding prognoses and end-of-life care is common, as is uncertainty surrounding treatment responses. Overall, key importance surrounds the use of more comprehensive methods to assess the value of cancer prevention, treatment, and supportive care to protect the vulnerable, to improve quality of life, and to empower decision making [7].

17.2 Value, Resource Scarcity, and The Iron Triangle of Healthcare Policy

Assessing costs, expenditures, and value in health-care involves the integration of several complex issues that surround utilization, clinical factors, patient characteristics, disparities of care, pricing, insurance coverage, supply and demand, and elements that characterize novel therapeutic interventions [10]. A description of *value* varies widely across healthcare systems and perspectives, summarized by the IOM with the following:

- Value includes patient preferences, quality, equity, efficiency, and product acceptability among a wide range of stakeholders (European Observatory on Health Systems and Policies);
- The value of a treatment is based on scientific value judgments, including clinical evaluation and an economic evaluation, and social value judgments, including considerations of efficiency and effectiveness (United Kingdom's National Institute for Health and Clinical Excellence); and
- The value of new and better medicine stems not only from the improved treatment of disease but also from a reduction in other healthcare costs, increased productivity, and better quality of life (Pharmaceutical Research and Manufacturers of America) [7].

Developing healthcare policy under conditions of resource scarcity requires both empirical and ethical considerations that consider the needs of specific patient populations with those of greater society in ways to maximize patient outcomes for resources that are consumed or, inherently, seeking to create value [10]. Representing this, the "Iron Triangle of Health Policy" presents the triad of cost, access, and quality of care to highlight the intricate reliance each of these individual factors plays in developing health policy (Fig. 17.1) [10, 11]. With unlimited wants and competing needs, marked difficulties are presented to comprehensively achieve lower costs, increased access, and higher quality of care particularly because an inverse relationship often exists between these elements (e.g., improving access and quality of care often occurs at the expense of higher costs) [10]. Adding to this, different stakeholders generally allocate different levels of importance to either cost, access, or quality of care. To illustrate, given most cost-sharing

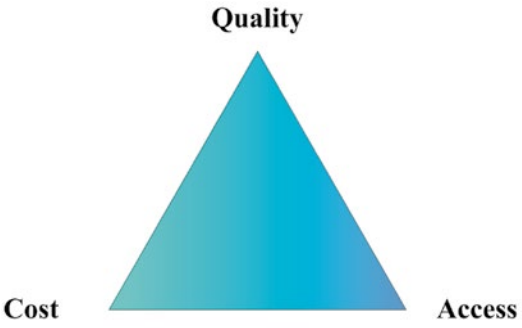

Fig. 17.1 The Iron Triangle of Health Policy (Source: Kissick [11]. Skrepnek [10])

healthcare coverage mechanisms, patients may demand the highest quality of care and access while deferring a majority of cost-containment issues to risk pools or payers. Conversely, primary payers (whether government, third party, employer, or individual) may predominantly demand cost-minimization or cost-containment without sacrificing either quality or access [10, 11]. Beyond health-care, overall public policy formation must also consider the broader impact and opportunity costs associated with appropriating resources either toward or away from prevention and treatment of various medical conditions and the potential productivity gains or losses to society that may result.

17.3 Systems Approaches to Defining and Achieving Quality in Health Care

Through the development of the structure-process-outcome paradigm, Avedis Donabedian (1966, 1980, 1982, 1985) emphasized the importance of broad, systems-based approaches when considering quality improvement in health care (Fig. 17.3) [12–16]. Within this paradigm, it was advocated that initiatives to improve care consider strategies that incorporated aspects of structure (e.g., attributes of various delivery settings), process (e.g., employing sound medical practices), and outcomes (e.g., the impact of interventions on a patient's health status). In more detail, *structure* involves attributes of an at-risk population, components of the system of healthcare delivery system (e.g., financing, organization, and availability of products or services), and the diverse physical, social, or economic environments surrounding patients, caregivers, and clinicians [12–16]. *Process* encompasses adherence to standards of care and involves an individual patient's health risks (e.g., behavioral, environmental, genetic) and the specific transactions that are involved in obtaining care (e.g., utilization, satisfaction). *Outcomes* are those relevant health status measures at a patient or population level that extend beyond morbidity and mortality to include effectiveness, efficiency, or equity. Over time, seven pillars of quality of care emerged from Donabedian's work: efficacy; optimality; acceptability; legitimacy; equity; cost; and efficiency [12–16] (Fig. 17.2).

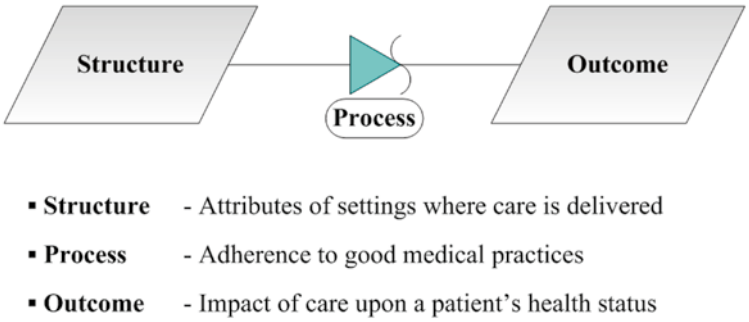

Fig. 17.2 Donabedian's Structure-Process-Outcome Paradigm (Adapted from Source: Donabedian [12–15])

▪ **Safe**	- Avoiding patient harm from medical care intended to improve outcomes.
▪ **Effective**	- Providing scientifically-sound services to all potential beneficiaries and refraining from those unlikely to benefit
▪ **Patient-centered**	- Providing respectful and responsive care according to an individual patient's preferences, needs, and values to ensure that these factors guide clinical decision making
▪ **Timely**	- Minimizing wait time and potentially harmful delays in care for both patients and providers
▪ **Efficient**	- Eliminating waste of scarce medical resources and time
▪ **Equitable**	- Providing care that does not differ across patient-specific attributes including gender, race or ethnicity, geographic location, or socioeconomic status

Fig. 17.3 Six Aims Targeted by the Institute of Medicine (IOM) to Improve Health Care Systems, 2001 (Adapted from Source: Institute of Medicine [17])

To address more current and persistent quality deficiencies, the IOM built upon Donabedian's work within the report *Crossing the Quality Chasm* to provide recommendations for safe, effective, patient-centered, timely, efficient, and equitable health care through a comprehensive system redesign (Figs. 17.3 and 17.4) [17]. Acknowledging the translational aspects that were also required to bridge experimental scientific work to that of real-world applicability, the IOM also defined *quality of care* as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." [17]. As such, this definition captures prevention and treatment of conditions to involve those outcomes desired by patients and other stakeholders, also incorporating changing and evolving standards of care. Expanding upon this, the IOM also emphasized three broad criteria through which structure quality improvement prioritizes: (1) impact; (2) improvability; and (3) inclusiveness (Fig. 17.5) [18]. Therein, the aspects of healthcare delivery that were noted to potentially impact quality included resources or capacities of facilities (e.g., volume of services, scope of services, access to technology, staffing levels, academic affiliation), characteristics of healthcare providers and systems (e.g., level of training, specialization), and the financing,

• **Impact**	- The magnitude of the burden attributed to a given condition within a population, to include morbidity, mortality, disability, and cost.
• **Improvability**	- The extent of the divergence between existing standards of care versus evidence-based approaches, and the likelihood that convergence be achieved and overall practice be improved.
• **Inclusiveness**	- The relevance of the priority area for improvement across a broad range of persons based upon key attributes of age, gender, race or ethnicity, geographic region, and socioeconomic status; the generalizability of quality improvement change across numerous disease states; and the capability and capacity for change across a range of diverse health care systems and providers.

Fig. 17.4 Three Criteria Used by the Institute of Medicine (IOM) to Identify Priority Areas for Improvement, 2003 (Adapted from Source: Institute of Medicine [18])

organization, and delivery of care (e.g., managed care, insurance mechanisms, regionalization of services) [18]. Additionally, it was recognized that a paucity existed in both the amount and strength of research relating to the structure-process-outcome paradigm in cancer. Although this issue persists, previously conducted research has reported associations between outcomes and structural components such as volume of cases, specialization, and provision of care [18].

The overall systems redesign framework offered by the IOM provided specific recommendations concerning prevention, acute care, chronic treatment, and palliative care in addition to supporting patient-centered quality improvement goals [18]. Summarily, the IOM's National Cancer Policy Board (1999) also recognized that optimal care may be compromised due to a patient's social and economic status, belief system, provider decision-making, or lack of healthcare coverage [4]. Internationally, three goals established by the World Health Organization for healthcare systems emphasized that: (1) health status across populations be maximized across the spectrum of one's life, to include end-of-life issues; (2) respectful treatment and orientation be addressed for patients, particularly concerning individual needs or preferences; and (3) financial protection be ensured by considering value propositions based upon an individual's ability to pay [19].

17.4 Health Outcomes and Comparative Effectiveness Research

Outcomes research broadly encompasses the measurement and assessment of the impact of medical conditions and interventions upon the health status of patients [20–22]. The Agency for Healthcare Research and Quality (AHRQ) emphasized:

> Outcomes research seeks to understand the end results of particular health care practices and interventions… End results include effects that people experience and care about, such as change in the ability to function. In particular, for individuals with chronic conditions - where cure is not always possible - end results include quality of life as well as mortality. By linking the care people get to the outcomes they experience, outcomes research has become the key to developing better ways to monitor and improve the quality of care. [20–22]

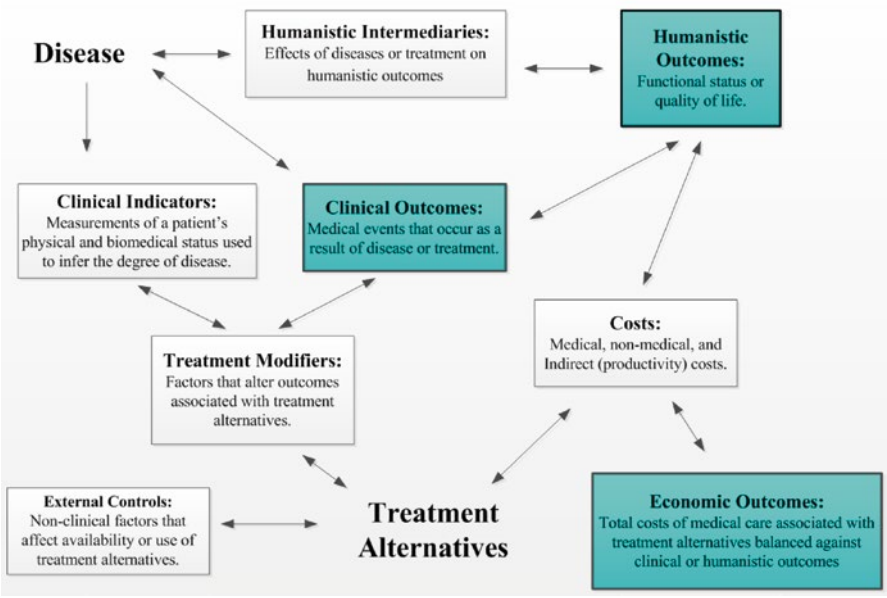

Fig. 17.5 The Economic, Clinical, and Humanistic Outcomes (ECHO) Framework (Source: Kozma et al. [25])

The National Cancer Institute (NCI) addressed outcomes research as a discipline which "describes, interprets, and predicts the impact of various influences, especially (but not exclusively) interventions, on 'final' endpoints that matter to decision makers" [21, 23].

Lipscomb et al. (2004) emphasized three requirements necessary for outcomes research to enhance the delivery of care: (1) developing valid and reliable outcome measures that were relevant for actual decision making; (2) providing supportive evidence that linked interventions to outcomes; and (3) developing an infrastructure necessary to translate empirical findings into pragmatic tools for decision makers [21, 24].

Presented in Fig. 17.5, a framework termed the ECHO model is often employed to encompass patient-centered economic, clinical, or humanistic outcomes [25]. Within this, *economic outcomes* involve the direct and indirect benefits attributed to a change in health state associated with treatment alternatives. *Clinical outcomes* involve those health-related events that occur subsequent to a medical condition or treatment intervention (i.e., morbidity or mortality), further classified as surrogate or intermediary endpoints (i.e., proxies of a person's health status) or final endpoints (e.g., cure, treatment success, progression-free survival, death). Finally, *humanistic outcomes* involve those factors potentially impacting opinions about the consequences of a medical condition or intervention upon a person's life or well-being and include utility, preferences, or health-related quality of life (HR-QoL), and patient-reported outcomes (PROs). Cost inputs to the ECHO model are those based upon varying perspectives of various decision makers or payers (i.e., "costs from the perspective of whom?"),

consisting of direct medical costs associated with the direct medical treatment of a given disease state, direct nonmedical costs associated with the ability to receive medical care including transportation or lodging, and indirect costs involving lost productivity including time off work [26]. Treatment modifiers are comprised of various factors that may influence the various outcomes of interest including, for example, adverse events or nonadherence. Notably, the ECHO framework often involves the simultaneous assessment of multiple types of outcomes that are often disease related.

An additional and important consideration within the ECHO model involves the distinct differences between surrogate endpoints or intermediaries versus final outcomes or end results, in particular, because several clinical intermediaries (i.e., results of laboratory tests) might only partially correlate to clinical morbidity of mortality outcomes or other outcomes that might be of key importance to patients themselves (e.g., quality of life, preferences, utilities) [21, 25, 26]. In a broad sense, also applied to goals of a comprehensive health system, several difficulties exist in ranking the various importance of either the types of final outcomes (e.g., economic, clinical, humanistic) or their corresponding intermediaries in a rank-order fashion to measure quality of care; Evans et al. confronted this issue by emphasizing that a key intrinsic goal of any health system simply remains one whose attainment is desirable in itself, irrespective of all others [27].

Specific to oncology, Lipscomb et al. (2004) emphasized that final outcomes are typically clinically oriented (e.g., overall survival, disease/progression-free survival, or relapse) though also embody humanistic measures (e.g., HR-QoL, perceptions of or satisfaction with care, patient preferences, economic utility) and economic outcomes (i.e., a monetized value of health status changes) [21]. Extending clinical outcomes to incorporate measures of both morbidity and mortality, the quality-adjusted life year (QALY) incorporates both survival with a measurement or estimation of economic utilities that reflect a patient's quality of life or preferences [28]. Further, Tate and Skrepnek (2014) also discussed the application of quality-adjusted time without symptoms or toxicity (Q-TWiST), an additional patient-reported outcome that adjusts survival measures with changes in quality of life [29]. Pursuant to an informal IOM survey on value assessments in cancer, Fig. 17.6 presents the diversity of conceptions and metrics that may be present [7].

Fig. 17.6 Attributes of Value Identified via an Informal Workshop Survey at the Institute of Medicine (IOM), 2009 (Adapted from source: Institute of Medicine [33])

Surrogate outcomes in cancer may include relevant laboratory data (e.g., hematologic or molecular responses) or disease changes (e.g., tumor shrinkage or disappearance), though other intermediate endpoints might involve screenings, smoking cessation, or the use of adjuvant therapies and various treatment protocols [21, 26]. While acknowledging these surrogate measures is crucial in assessing the quality of patient care, a need is also present to understand and quantify correlates between intermediaries and final outcomes. As noted by Lipscomb et al. (2004) and Skrepnek (2005), a key corollary of an observed improvement in either clinical or intermediate outcomes is that of prediction of success in improving end results of care [21, 26].

Given that the majority of outcomes research in cancer tends to focus upon screening, diagnosis, and treatment interventions, it is emphasized that its contributions (particularly the emerging roles of PROs) cross the continuum from prevention and early detection to survivorship and end-of-life care [7, 21, 30]. While more consensus exists surrounding the definition and measurement of final outcomes, despite notable exceptions (e.g., defining disease- or cause-specific versus relative survival), considerable discussion surrounds the appropriate assessment particularly of humanistic outcomes including utility, PROs, and satisfaction [21].

A central tenet of the 2010 Patient Protection and Affordable Care Act (ACA), comparative effectiveness research (CER) emerged as an approach to increase the efficiency and amount of comprehensive evidence-based information available to inform patients and providers within the US healthcare system [30, 31]. Several methodological approaches inherently comprise CER, though the general empirical premise emphasizes real-world investigations of representative populations, personalized interventions, patient-centered outcomes, and active treatment comparators as opposed to placebo controls. More formally addressed by the IOM, CER involves the "generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels" [32, 33].

Clinical evidence within CER is categorized as either primary or secondary. *Primary clinical evidence* involves the direct reporting of new empirical findings through experimental or quasi-experimental studies to include a range of clinical trials (e.g., pragmatic, cluster randomized, large simple clinical trials) or observational studies (e.g., retrospective case-control or cohort studies) [31–33]. While prospective data collection may be involved, existing data sources (e.g., electronic medical records, administrative claims data, registries) are also considered. *Secondary clinical evidence* in CER involves the systematic collection and synthesis of primary research findings, essentially pooling results from multiple investigations to support conclusions with improved statistical power (e.g., meta-analyses, decision-analytic modeling, mixed treatment comparators) [31–34].

Despite the recognition that the Patient-Centered Outcomes Research Institute (PCORI) was formalized partially in response to increasing healthcare expenditures, CER explicitly omits assessments of costs (either by way of resources consumed or in terms of a monetized change in health status) as defined within the ACA

[30]. The challenges and controversies associated with health state valuations and concerns of rationing have emphasized the role of CER as providing outcomes evidence that may be used within other health economic or cost-effectiveness investigations [26, 28, 30].

17.5 Comprehensive Economic Evaluations: Cost-Effectiveness, Cost-Utility, and Cost-Benefit

Despite the intuitive rationale to study outcomes to improve quality of care in cancer, measuring economic, clinical, or humanistic outcomes alone does not afford an opportunity to assess or specify which interventions might most efficiently improve care across diverse populations or circumstances [26, 35]. A complete framework to evaluate the value of innovative treatment interventions in terms would seek to assess both resources consumed and outcomes achieved of novel approaches versus appropriate clinical alternatives, illustrated in Fig. 17.7 [10, 26, 36].

Expanding the scope of CER to include both costs and outcomes of alternative treatments, health technology assessments and pharmacoeconomic analyses are inherently based upon principals of cost-benefit analyses, welfare economics, and game theory [10, 26, 36]. Applied specifically to the use of pharmaceutical services or products, *pharmacoeconomics* is characterized by the comprehensive identification, measurement, and comparison of healthcare resources consumed and various patient outcomes for novel interventions compared to existing standards of care [26, 36]. Given that a principal goal of these analyses is to yield the greatest patient benefit in terms of outcomes for every healthcare dollar expended, the formal framework identifies opportunity costs gained or lost and, therefore,

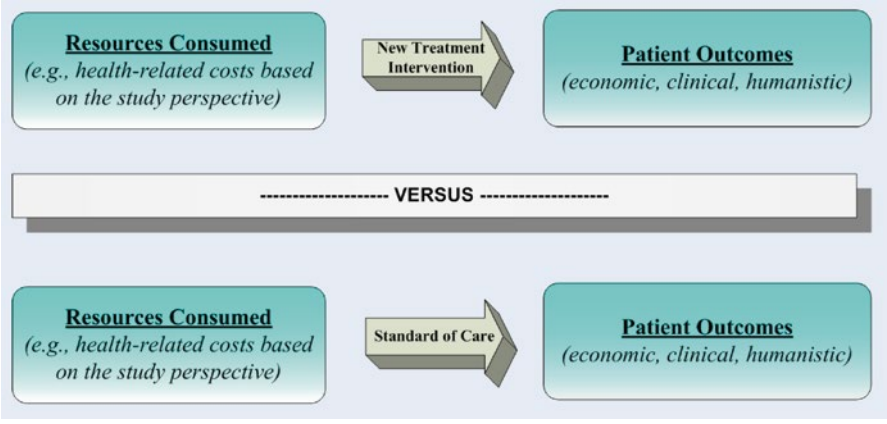

Fig. 17.7 General Study Design Framework of Health Technology Assessment or Pharmacoeconomics (Adapted from Source: Bootman et al. [36]. Skrepnek [10])

provides decision makers a theoretically sound approach to address the role of emerging healthcare innovation within the health policy triad of cost, quality, and access [10, 26, 36]. Across the continuum of cancer, value propositions ranging from prevention to survivorship may consider numerous specific stakeholders (e.g., providers, payers, patients), or society overall. Particularly from the societal perspective, the most effective, efficient, and equitable use of innovation would be afforded via an optimal balance of costs and benefits to afford the greatest net benefit across an entire population [26]. Comprehensive assessments of costs and outcomes across treatment alternatives uniquely augment evidence-based decision making when considering pressures of cost-containment, resource scarcity, increased expenditures, and treatment advances [10, 26].

Essentially, this methodological approach may provide a more robust assessment of quality and to augment value-based competition when considering expanding treatment options and increasing healthcare utilization and cost. Therein, value propositions of healthcare innovations are deemed "cost-effective" under three scenarios, when the novel approach is either: (1) less expensive and at least as effective as existing standards of care; (2) less expensive and less effective, though only if an extra benefit is not worth an extra expense; or (3) more expensive and more effective under conditions that the additional health outcome benefit is worth the additional cost, up to a certain opportunity cost threshold value [26, 28].

Overall, the various types of studies that comprise health technology assessments or pharmacoeconomics are presented in Fig. 17.8. Notably, full economic analyses are designated with cost-effectiveness, cost-utility, or cost-benefit analyses and may be best characterized by their application of incremental calculus and

	Inputs *(costs,based on perspective)*	**Outputs** *(outcomes,always patient-oriented)*
• **Outcomes Assessment**	-----	Economic ,Clinical,or Humanistic
• **Cost of Illness**	$	-----
• **Cost-Consequence Analysis (CCA)**	$	All relevant outcomes *(each reported separately)*
• **Cost-Minimization Analysis (CMA)**	$	Assumed Equal
• **Cost-Effectiveness Analysis (CEA)**	$	Natural Units *(i.e.,clinical)*
• **Cost-Utility Analysis (CUA)**	$	Utility or Preferences, Humanistic Outcomes *(Quality-Adjusted Life Years,QALY)*
• **Cost-Benefit Analysis (CBA)**	$	$ *(change in health state valued in monetary terms)*

Fig. 17.8 Selected Types of Health Technology Assessment or Pharmacoeconomic Study Designs

subsequent measurement of opportunity costs to compare both costs and outcomes for new interventions versus existing standards of care.

Addressed previously, even though economic analyses provide information to maximize patient outcomes when resources are limited, ethics or morals may be not be comprehensively captured within all specific types of assessments conducted. As Dougherty (1993) stated, "an ethical imperative to save individual lives even when money might be more efficiently spent to prevent deaths in the larger population" is often characteristic of the types of interventions offered within rare, progressive, or terminal diseases, more formally called the *rule of rescue* [28, 37]. Continued assessments of both ethical and economic issues that are involved in the adoption and reimbursement of novel interventions are warranted across rare, progressive, and terminal conditions in light of new advances in screening or diagnostic procedures and personalized or targeted therapeutics [28].

17.5.1 Burden or Cost of Illness (BoI, CoI): Budget Impact Analysis (BIA)

Burden or *Cost of Illness* (BoI, CoI) analyses predominantly seek to identify costs consumed (e.g., those associated with treatment), but may extend to include work loss, morbidity, and mortality [38–41]. Therefore, outcomes may be measured but are usually not formally analyzed with costs. Overall, these investigations may be useful to bring awareness to the impact that a given disease or health state may have upon patients, payers, or society to assist decision makers to allocate appropriate budgets, to estimate payment structures, or to better understand trends in care. BoI/CoI studies that focus on long-term costs at the patient level may additionally provide key inputs to other economic studies. Presented in Fig. 17.9, Lipscomb et al. (2004) offered a conceptual framework to cost cancer-related healthcare episodes that spans precancer cases through end-of-life care to organ acquisition or donation [42].

The categorization of BoI or CoI studies involves two parts: (1) prevalence versus incidence models and (2) excess versus attributable costing [39, 40]. *Prevalence models* are cross-sectional in nature, reflecting costs in a given time period (e.g., annual) and comprising the most common approach. Conversely, *incidence models* involve lifetime costs (i.e., spanning from the onset of disease to cure or death), typically requiring estimation of future costs associated with a given disease. In *excess costing*, a case-control methodology is used wherein those with a specified condition are matched or compared against a control group without the disease, or simply compared to an overall or available population. Thus, results reflect the additional impact that occurs as a result of having a given condition or disease. The *attributable costing* method uses a case-series approach where a burden of illness is measured only among those with a given disease. While results seek to report overall resource utilization and costs associated with any given disease state, the attributed BoI study may separately report selected subgroups or comorbid conditions, essentially borrowing elements of excess costing.

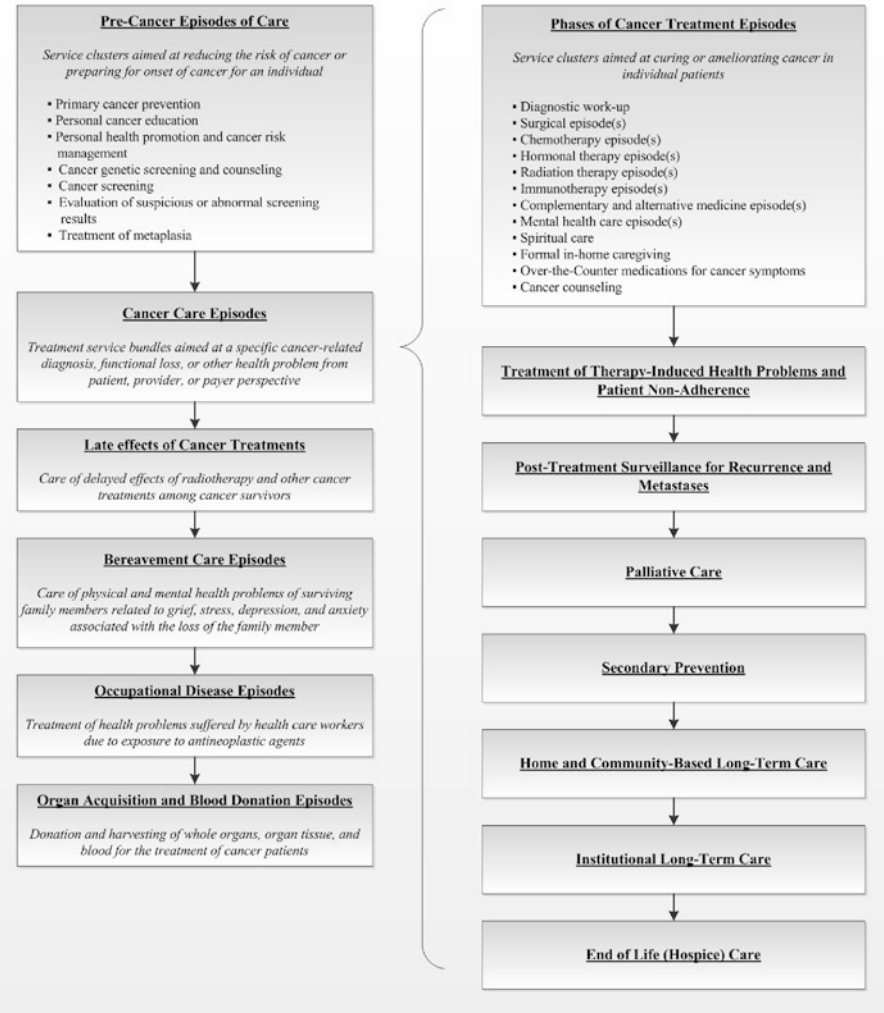

Fig. 17.9 A Conceptual Framework for Costing Cancer-Related Health Care Episodes (Source: Lipscomb et al. [42])

A pragmatic approach used to apply findings, in part, from BoI/CoI studies may include a *budget impact analysis* (BIA) [43, 44]. BIAs seek to measure the net cost of treatment associated for any given number of type of patient within specific healthcare settings or patient population. Historically, although BIAs often focus on specific healthcare services or pharmacy expenses, comprehensive direct medical costs may be incorporated by implementing broad comparative cost determinations across competing scenarios (e.g., single or multiple therapeutic areas or diseases).

17.5.2 Cost-Consequence Analysis (CCA)

Cost-consequence analyses (CCA) measure all relevant costs and outcomes, though only list values without formally incorporating outcomes in a comprehensive fashion [45, 46]. Therefore, responsibility is placed upon the decision maker to analyze data and draw comparisons of efficiencies associated with any given innovation relative to any standard of care. While the CCA may promote transparency within full economic analyses, in themselves these investigations are rarely stand-alone given concerns that inappropriate conclusions may be drawn concerning the information presented.

17.5.3 Cost-Minimization Analysis (CMA)

A *cost-minimization analysis* (CMA) assesses differences in costs (measured in dollars and based upon the perspective of a study's selected payer of an innovation versus a reference standard of care) while assuming that patient outcomes or health benefits are equivalent [45, 46]. Given this, the approach is a straightforward concern of assessing costs, though requiring that the equivalency of outcomes be firmly established (e.g., via clinical trials, particularly those designed to establish equivalence). Though intuitive in its interpretation (e.g., dollars saved), controversy does surround a definition of equivalency in outcomes, particularly if the measurement of an economic, clinical, or humanistic outcome may potentially differ across treatment options, or if equivalence is derived via subjective means [46]. Further, clinical efficacy measured from experimental, randomized clinical trials may poorly translate to real-world effectiveness in which the CMA often seeks to address.

Given that the objective of the CMA is to assess costs and not to compare health outcomes, researchers may not necessarily designate the method as a full economic analysis [47]. Even though the approach may remain a conceptually weaker form of pharmacoeconomic evaluation, the strength of results emanating from a CMA center upon the strength of evidence that outcomes are indeed the same – a presumption that may be inadequately addressed especially with regard to humanistic outcomes including preferences.

17.5.4 Cost-Effectiveness Analysis (CEA)

Cost-effectiveness analyses (CEA) comprise perhaps the most commonly used full economic method in the United States to compare relative cost and benefits of treatment interventions [26]. Overall, costs are measured first in physical units and subsequently valued in monetary units based upon the study's payer perspective. The outcome of effectiveness is measured in natural units of health improvement, which can include, for example, clinical outcome measures, life years gained (LYG), progression-free survival, prevention of an event, or treatment successes. The approach is often viewed with preference particularly among clinical decision makers, as researchers do not have to explicitly place a dollar value upon outcomes, and therefore

can compare treatment options when it is impossible (or inappropriate) to monetize changes in health status. Although different treatments can be compared that have the same treatment goals, only options that have the same type of outcome can be measured, and only one outcome can technically be measured at a time. Thus, the CEA cannot differentiate between two treatments that have two disparate outcomes (e.g., years of life gained versus disability days avoided). Further, not all treatments have similar measureable intermediate or surrogate outcomes.

Results of the CEA may be initially presented numerically, the hallmark of which is an incremental cost-effectiveness ratio (ICER) that compares the difference in both costs and effects of an innovation versus a comparator as [26]:

$$ICER = \frac{\Delta \text{TotalCosts}}{\Delta \text{Effect}} = \frac{\text{TotalCosts}\left[\text{new intervention}\right] - \text{TotalCosts}\left[\text{referent, standard of care}\right]}{\text{Effect}\left[\text{new intervention}\right] - \text{Effect}\left[\text{referent, standard of care}\right]}$$

The ICER is interpreted as the cost per additional unit of effect and is reflective of the opportunity costs necessary to obtain a set increase in outcomes vis-à-vis an existing standard of care [26, 28]. In a theoretical sense, the ICER obtained from any given investigation is compared to an individual payer's ICER threshold, *RT* or λ, which reflects a willingness-to-pay or willingness-to-accept level for value determinations [28]. Therein, cost-effectiveness may be established when $RT < ICER$, indicating that an observed innovation's ICER is less than the payer's threshold (i.e., value for the money) [28].

Graphically, common approaches to present the results of CEAs may include the cost-effectiveness plane or a cost-effectiveness acceptability curve (CEAC) [26, 48]. The cost-effectiveness plane (Fig. 17.10) compares a standard of care at the point of origin to the medical innovation under investigation based upon two dimensions: cost and effect. If a new intervention yields a lower total cost and higher effect than the standard of care, it is always deemed cost-effective and appears within the lower right-hand quadrant of the plane; the designation of this form of technology is that of "dominance." Conversely, if a novel intervention yields a higher total cost and provides worse outcomes than the standard of care, it is never deemed cost-effective and is denoted "dominated," appearing in the upper left-hand quadrant of the plane. The other two quadrants involve trade-offs – either the innovation costs more and has an improved effect (i.e., top right-hand quadrant), or the innovation is cheaper and has a lower effect (i.e., bottom left-hand quadrant). In situations involving these types of trade-offs, interpretations of cost-effectiveness may not entirely be straightforward, because the level of a given payer or patient's willingness to pay or willingness to accept for a given change in the outcome becomes the principal decision criterion that defines whether the novel intervention is value producing. Again, an intervention is considered cost-effective when it is found to be either: (1) less expensive and at least as effective as existing standards of care; (2) more expensive and more effective than existing standards of care when the additional health benefit is viewed as being worth the additional cost; or (3) less expensive and less effective than an existing standard of care in instances where any extra health benefit provided by innovation would not be viewed as worth the extra expense [26].

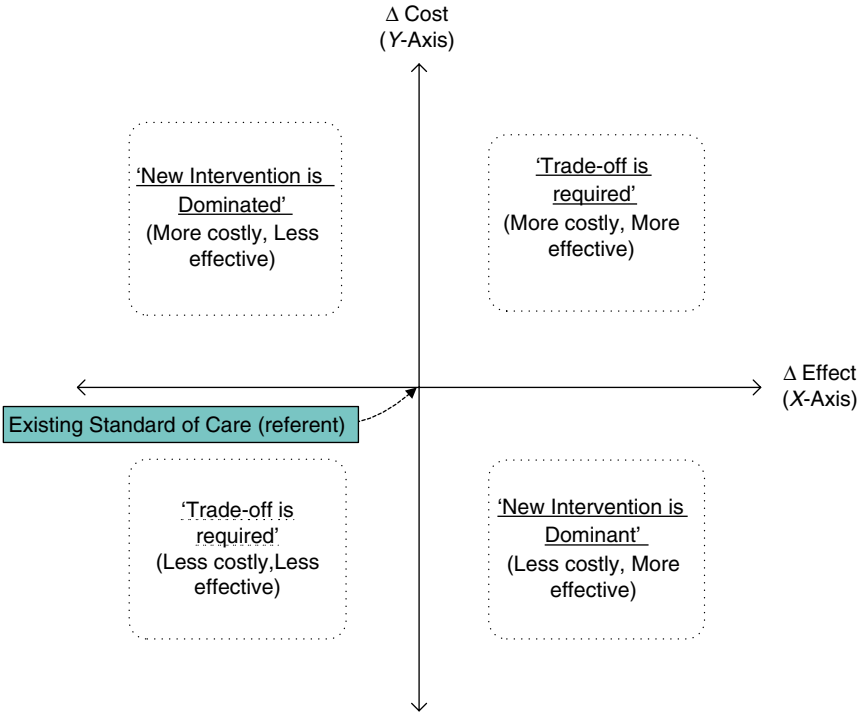

Fig. 17.10 The Cost-Effectiveness Plane to Graphically Depict Cost-Effectiveness Analyses (CEA) (Adapted from Source: Skrepnek [26])

17.5.5 Cost-Utility Analysis (CUA)

Cost-utility analyses (CUA) builds upon economic utility theory that extends CEAs to incorporate a patient outcome that seeks to capture elements of morbidity and mortality (i.e., both the quantity and quality of life) [45, 46]. A standardized measure is assessed across treatment comparators, known as a quality-adjusted life year (QALY) [28, 45, 46, 49, 50]. The QALY formally incorporates measures or proxies of *utility*, a concept that represents a perceived ability to satisfy one's needs or wants. Formalized by von Neumann and Morgenstern (1953) in their seminal work on game theory, utility involves preferences among alternatives and is incorporated within the QALY as [28, 45, 46, 51]:

$$QALY = \left(\text{Life Expectancy via LYG}\right)\left(\text{Health State or Preference via Utility}\right)$$

The potential strengths of incorporating an estimate or proxy for utility in economic analyses of outcomes become particularly important when considering a patient-centric approach to treatment that predominantly improves the quality of life for an individual [45, 46]. To illustrate, in supportive cancer care, treatment options that consider patient preferences which may largely impact an individual's

well-being (versus improving progression-free survival) could not otherwise be appropriately captured within a CEA assessing life years gained. Alternatively, CUAs also capture outcomes wherein treatment options may extend life, though the quality of that life is diminished. As a single outcome measure is used in a CUA, results may compare markedly different intervention options (both health care and non-health care) through which to evaluate economic efficiency. Overall, CUAs may be advocated when quality of life is an important outcome, but may not necessarily be required if effectiveness closely correlates to quality of life or if only surrogate outcomes can be obtained. The assessment of utility or patient preferences remains complex and is often reliant upon the specific approach being used and the population being studied. Continued research is required to best understand how to best apply issues of ethics and justice within the CUA framework, how to incorporate varying levels of a patient's risk aversion or negative measurements of utility, and which referent states are deemed most appropriate.

Three common methods are used in eliciting either patient preferences or utility: (1) rating scales (RS), which yield preferences; (2) time trade-off (TTO), which also yields preferences; or (3) standard gamble (SG), which estimates utilities [45, 46]. Notably, the derivation of preferences may also be undertaken with selected health-related quality of life measures, including the Health Utilities Index (HUI), EQ-5D, and SF-36, among others [52–55]. Appearing in Fig. 17.11, a *rating scale* (RS), or visual analog scale (VAS), establishes that endpoints are anchored by the "best imaginable health state possible" (or, alternatively, "perfect health") versus the "worst possible health state imaginable" (or "death") [45, 46]. Other health states are explained and subjects are asked to rate those states between these two endpoints. Therein, several health state options and interventions may be evaluated, with raters expressing preferences for each upon a single, uniform scale. In the *time-trade-off* (TTO), respondents are offered two alternatives, to be in: (1) disease state *i* for time *t*, followed by

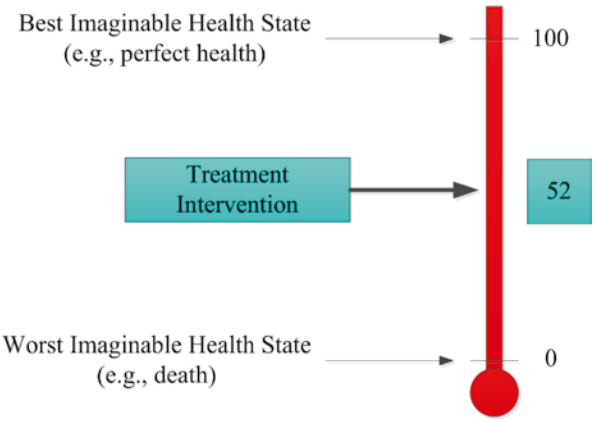

Fig. 17.11 The Rating Scale (RS) or Visual Analog Scale (VAS) to Measure Preference (Adapted from Source: Drummond et al. [45]. Bootman [46])

death; versus (2) healthy state for time x (less than t), followed by death (Fig. 17.12) [45, 46]. Essentially, and often incorporating a rating scale in its measurement, the time within the best imaginable health state, x, is varied until the respondent reports indifference between the two scenarios to yield their preference for a given treatment intervention. Finally, the *standard gamble* (SG) in Fig. 17.13 is again the formal expression of the von Neumann-Morgenstern expected utility theory, which incorporates a dimension of risk and presents a key strength of the method [45, 46, 51]. Thus, the SG estimates utility, rather than that of patient preference alone. Building upon the TTO, the SG offers the respondent two scenarios: (1) a gambling scenario that involves a treatment with two possible alternatives to offer a patient movement directly toward a healthy life for x years versus the probability of immediate death; and (2) scenario two which is to remain in disease state i for the remainder of their life. Essentially, a lottery is conducted using a probability wheel (Fig. 17.14) until indifference is expressed between a certain outcome versus a probabilistic outcome as:

$$U_{CertainHealthState} = \left\{p \cdot U_{PerfectHealth}\right\} - \left\{(1-p)U_{Death}\right\}$$

where U = utility and p = probability [51].

Overall, even though the SG is typically viewed as the gold standard to elicit utilities, the RS measurement of preferences remains the easiest to use, and the TTO remains conceptually easier than the SG [45, 46]. Values obtained from the measures also vary, with the RS generally yielding the lower preference values [56].

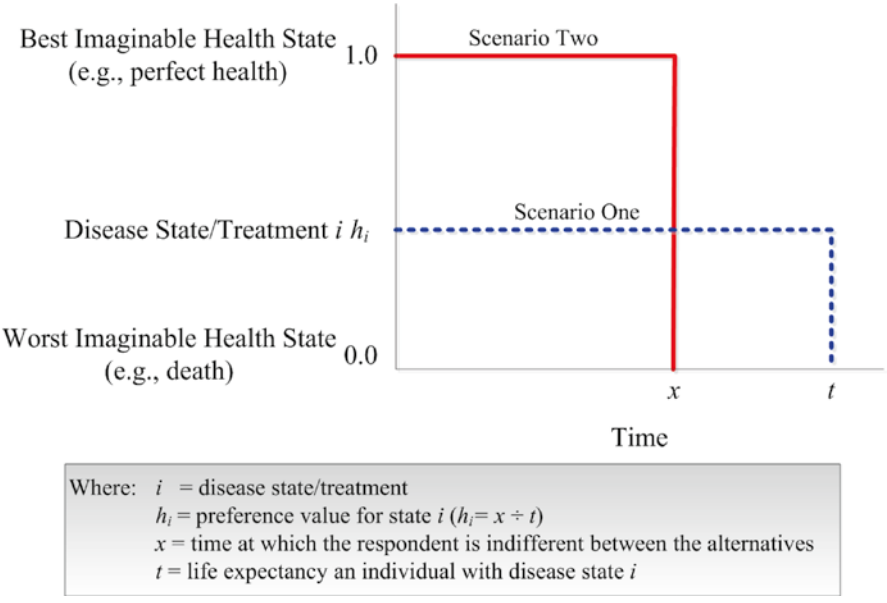

Fig. 17.12 Time Trade-Off (TTO) to Measure Preference (Adapted from Source: Drummond [45]. Bootman et al. [46])

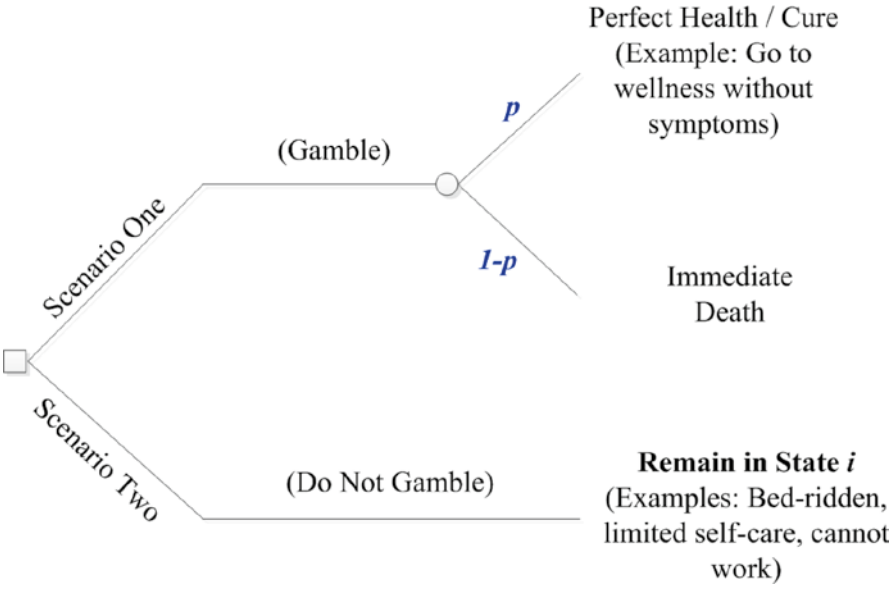

Fig. 17.13 The Standard Gamble (SG) to Estimate Utilities (Adapted from Source: Drummond [45]. Bootman et al. [46])

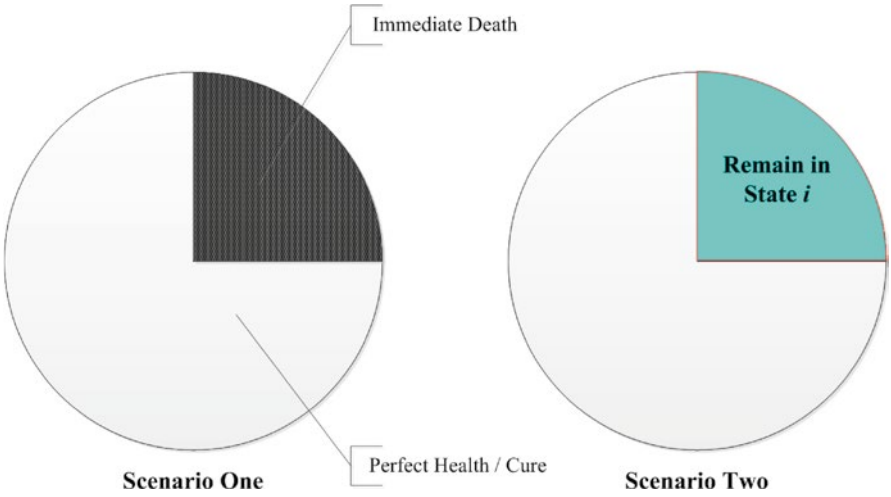

Fig. 17.14 The Probability Wheel Representing the Standard Gamble (Adapted from Source: Drummond [45]. Bootman et al. [46])

Administration of the survey instrument to varying groups may also result in different estimates [46]. To illustrate, even though health professionals might understand the disease well, their response sets may differ substantially from those that currently have a given disease or those that may have moved to survivorship. While the

general public may offer a societal view, these persons may poorly understand the true impact of a given condition. Furthermore, in many scenarios, proxy respondents that are caregivers may often be preferred if persons with conditions are either pediatric or older, if persons with a disease are unable to participate, or if patient coping mechanisms might bias observations. Much remains to determine which of the various methodologies are best suited.

17.5.6 Patient-Reported Outcomes (PROs) and Health-Related Quality of Life (HR-QoL)

In the context of a CUA, quality of life presents as a key component through which cost-effectiveness is evaluated [46]. The importance of capturing patient-reported outcomes (PROs) involves a realization that several effects of treatments may be known only to the patient him or herself and that patients provide unique and important perspectives involving the evaluation of various medical interventions. Formally capturing this information is also more valid and reliable when done using accepted scientific principles versus informal interviews or assessments.

Importantly, *patient-reported outcomes* (PROs) is a broad term that describes a disease or treatment outcome that is subjectively reported by the patient [57]. Examples of PROs include the assessment of pain, discomfort, patient adherence, signs and symptoms, satisfaction, or health status [58]. *Health-related quality of life* (HR-QoL), more specifically, refers to the impact of disease on an individual's functioning and well-being. HR-QoL is, therefore, a type of PRO and is often multidimensional in nature [57].

When measuring HR-QoL, either *generic* or *disease-specific* instruments can be considered [57]. Generic, or general, instruments can be applied across numerous diseases or conditions, varying medical interventions, and different populations. *Preference-based* generic instruments involve population-derived preferences, typically yielding health index scores that range from 0 to 1. Examples of preference-based generic instruments include Health Utilities Index (HUI), EuroQol (EQ-5D), and Quality of Well-Being (QWB) scale [52–54, 59, 60]. *Health-profile* generic instruments usually involve multiple domain scores that provide a summary score and can be patient specific in nature. Examples include the SF-36, Sickness Impact Profile (SIP), and Nottingham Health Profile (NHP) [55, 61–65].

Providing more detail, the EQ-5D consists of two main components, the: (1) descriptive system; and (2) self-rating [53, 54]. The descriptive system essentially describes some 243 health states (plus death and unconsciousness) across five dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which is comprised of three levels (i.e., (1) no problems, (2) some problems, or (3) severe problems). Importantly, the descriptive system is linked to population-based preference weights. The second component of the EQ-5D, the self-rating, utilizes a visual analog scale to produce an assessment of health status that emanates from the individuals themselves. The SF-36, a common health profile that also allows researchers to compare results to population norms, captures eight domains measured

across 36 items: general health; physical functioning; social functioning; role function limitations – physical; role function limitations – emotional; mental health/emotional well-being; energy/fatigue or vitality; and bodily pain [66]. Versions of the SF-36 are available that utilize validated algorithms to extrapolate findings as approximations of utility (i.e., the SF-6D) [67, 68].

Specific to cancer, an extensive array of disease-specific PRO and HR-QoL instruments have been developed [42]. The FACT-G, or General Functional Assessment of Cancer Therapy, was developed to provide assessments across several types of cancer, for example, the FACT-L for lung cancer, the FACT-B for breast cancer, and the FACT-O in ovarian cancer [69–72]. Additionally, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30 (EORTC QLQ-C30), also provides for the assessment of quality of life in cancer patients, with additional modules for both specific types and treatments, including palliative care [73, 74]. Funded by the National Institutes of Health, the Patient Reported Outcomes Measurement Information System (PROMIS) offers standardized self-reported measurements across several domains (i.e., physical health, anxiety, depression, fatigue, sleep disturbance, social function, pain interference, global health) for chronic disease and within cancer- and supportive care-specific populations [75–77]. In certain instances, the use of clinical and functional observation reports by providers may also offer information concerning HR-QoL via adverse event identification and staging, illustrated via the National Cancer Institute Common Terminology Criteria for Adverse Effects (NCI CTCAE) [78]. Importantly, the NCI Symptom Management and HR-QOL Steering Committee recently recommended a core set of symptoms to be considered within adult cancer trials where PROs are measured including fatigue, insomnia, pain, anorexia, dyspnea, cognitive problems, anxiety, nausea, depression, sensory neuropathy, constipation, and diarrhea [79].

17.5.7 Cost-Benefit Analysis (CBA)

The goal of a *cost-benefit analysis* (CBA) is consistent with many forms of either economic or financial analyses: to identify if an intervention's future benefits in today's dollar terms exceed costs, thereby making the program worthwhile (i.e., due to the provision of a positive net benefit) [45, 46]. Applied to health outcomes research, the CBA measures costs in dollars and places a monetary value on the change in health state (i.e., benefit) associated with a novel intervention versus a standard of care. Stated differently, the incremental costs of an intervention versus a comparator are evaluated in terms of its incremental discounted future benefits, the difference of which is the net benefit (or loss) in present value (PV) terms as:

$$\text{Net Benefit} = \text{PV(Benefits)} - \text{PV(Costs)}.$$

Three types of health status benefits may be captured within the scope of a CBA: (1) *direct* benefits reflecting monetized changes in a health state associated with the utilization of a healthcare innovation; (2) *indirect* benefits associated with a

potential increase in productivity (e.g., earnings); and (3) *intangible* benefits capturing the psychological benefits of improved health [45, 46]. The methods used to quantify these predominantly include either human capital or willingness-to-pay approaches. *Human capital*, historically a common methodology in economics, presumes that the worth of health benefits is captured in the economic productivity that is permitted by a new intervention [45, 46]. Therefore, the ramifications of any given disease are distilled in losses in productivity. Even though the valuations of productivity are based upon the discounted lifetime value of expected earnings and nonmarket activities (e.g., household work) may also be captured, controversy exists in the valuation of pain and suffering or leisure time. Furthermore, human capital does not consider what consumers or payers are willing to pay or sacrifice for a given intervention (i.e., the consumer's view of opportunity costs). *Willingness-to-pay*, or contingent valuation, is a form of stated preference wherein respondents are asked to quantify a nonexistent or hypothetical market (contingent market) to generally assess what their willingness to pay would be to reduce the chance to avoid an adverse health outcome. Beyond the two aforementioned, revealed preferences may also be considered in quantifying health status benefits, most typically with life insurance or actuarial tables that capture wage-risk information (i.e., the trade-offs that occur in salaries involving occupational hazards or risks).

The primary goal, again, of the CBA is to assess if a positive net benefit exists, wherein interventions may also be rank ordered to yield the most economically efficient programs [45, 46]. The CBA is often viewed as being potentially the broadest and most robust analytic framework allowing for the measurement and comparison of markedly disparate types of programs and consequences (e.g., cancer prevention campaigns versus public works programs). Though recognizing that the methodology provides an absolute worth associated with an intervention without requiring information concerning one's willingness-to-pay or reimbursement threshold, the strength of a CBA often becomes fully realized when the analyst assesses externalities (i.e., spillover benefits of an innovation that goes to other members of society, referred to as *Kaldor-Hicks efficiency*) [10, 45]. Typically, CEAs and CUAs poorly incorporate the effect of spillovers within their framework [45, 46].

Concerning the usefulness of CBAs in health care, while the method is conceptually easily understood, difficulty and controversy may arise in valuing health-related outcomes in monetary terms [46]. To illustrate, while a final outcome may be valued with some level of certainty (e.g., life years gained), an intermediate outcome such as treatment response may suffer from validity or measurement issues to include reliability and precision. Overall, a CBA is often reserved for studies wherein the patient health outcomes of interest may possibly and appropriately be monetized in dollar terms [46].

Conclusion

Achieving a cancer care system that is effective, efficient, and equitable remains both a priority and a challenge among providers and policy makers. While various definitions of quality and value exist, both cost and access remain of central concern. Through comprehensive health technology assessments or pharmacoeconomic analysis, empirical evidence seeks to maximize patient-centered outcomes

for each resource expended across the continuum of cancer, also providing a formal and robust approach to directly incorporate patient preferences. The careful balance between infinite wants and finite resources warrants continued empirical evidence to guide healthcare systems toward optimal effectiveness, efficiency, and equity.

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Hospitality Houses for Cancer Patients: The Editha House Perspective

18

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It is an understatement to say that cancer diagnosis interrupts patients' lives and leaves them experiencing a wide range of emotions including fear, concern, anger, sadness, and an overwhelming sense of feeling lost within the world. Despite all of these emotions, one overall theme has been identified as central to the experience: patients are willing to do *whatever it takes to fight cancer* [1]. This strength and determination is central to the experience of guests at Hospitality Houses across the nation and especially at Editha House in Phoenix, Arizona. While experiencing the emotional rollercoaster of cancer diagnosis and treatment, Hospitality Houses provide patients with an environment of supportive care to aid and encourage them during their experience.

This chapter discusses the ways in which Hospitality Houses, specifically Editha House, play an important role in the ability for cancer patients to avoid travelling great distances to treatment centers, access social support, and alleviate financial strain, while residing in healing environments and providing their caregivers with essential support.

One of the first decisions patients must make is *where* they will undergo treatment. For patients living within close range to medical facilities or hospitals, their treatment decisions are frequently determined by distance to treatment facilities [2]. Many times, patients will choose treatment centers that are closer to their homes to ease their burden. Others will travel outside of their communities, especially if they are interested in obtaining a second opinion, participating in a clinical trial, or trying

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a different form of treatment not offered in their community. Yet, for rural patients, who do not live near treatment centers, some will forgo treatment altogether.

The burden of attempting to navigate around unfamiliar territories while locating adequate housing and transportation is daunting on top of dealing with a cancer diagnosis. One study of lung cancer patients in New Hampshire and Vermont found that patients living further from radiation therapy centers were less likely to receive radiation for their disease [3]. Another study found that women with early-stage breast cancer living more than 20 miles from a radiation treatment facility were not only less likely to have breast-conserving surgery but also significantly less likely to receive postoperative radiation that would reduce their risk of recurrence [4]. Moreover, it has been found that lung cancer patients living further from thoracic surgery hospitals were less likely to receive surgery, and both lung cancer and rectal cancer patients that lived distant from medical facilities were less likely to receive chemotherapy [2]. These rural patients are faced with the stress of cancer diagnosis and the additional strain of travelling great distances to access treatment [5, 6]. Due to the increased travel burden, evidence suggests that there is an increased risk of cancer mortality for rural patients [5]. Cancer treatment centers that require longer than average patient journeys all showed an inverse association between travel time and treatment obtained [2, 7].

Why is it important to examine the relationship between travel distance and survival? Distance to treatment centers affects the likelihood of cancer reoccurrence and the amount of treatment received [2]. While this influence may seem initially surprising, the impact becomes clear when one imagines newly-diagnosed individuals travelling outside of their communities into new and unfamiliar places in order to obtain treatment. When cancer patients lack supportive care and must travel to seek treatment, they are often left wondering where they will be able to live and find supportive resources. Relocation is a cumbersome ordeal [7]. When combined with a cancer diagnosis, it confronts both the patient and patient's caregiver with a surreal and stressful experience. It is at this beginning point when patient lodging plays a pivotal role in the amount and type of treatment received. Therefore, it is an important arena to further understand because it can be the difference between life and death for many patients.

Hospitality Houses provide lodging to patients and their caregivers who are receiving medical care away from their communities. These facilities help alleviate the financial burden often associated with medical crises and have shown to reduce stress for patients and family members, resulting in better survivorship rates and quality of life [1, 4, 8–12]. Unlike a hotel, Hospitality Houses afford opportunities to those experiencing similar medical situations to come together as a community and support one another. In particular, Editha House emphasizes an environment that feels like *home* with private kitchens, bedrooms, bathrooms, and common living areas and common kitchens throughout the House. Editha House, at its Phoenix location, is also equipped with private patios and an organic community garden, so patients can receive therapeutic benefit from the serene and tranquil environment [13]. Patients have the option of finding support among others in similar situations by utilizing the common areas, and if they are not feeling well or simply

want privacy, they have the option of retreating to the comfort of their private units. The overarching goal is to provide patients with a "home away from home," so that they may focus on healing [14].

Hospitality Houses are designed with the patients' needs in mind. While all are different from one another in design and services offered, they frequently assemble a multitude of resources with the intention of reducing the burden of travel on patients. For example, the act of relocating requires patients to identify local resources. Editha House's Phoenix location is currently staffed 24 hours a day, 7 days a week, so staff are able to provide guests with community resources and aid them in navigating their new environment. This is commonly referred to as *instrumental social support* [12] and is proven valuable because it provides patients with practical information and assistance that may help patients cope more effectively with treatment and other cancer-related life stressors.

Research has also indicated that social support plays an important role in patient survivorship. Women with low levels of social support are linked to poorer quality of life, while women with stronger social support networks are linked to reduced stress and improved survival rates [11, 14]. Furthermore, studies show that social support acts as a buffer to protect individuals from the negative influence of stress-related biological processes [12]. For example, ovarian cancer patients with high levels of support networks exhibit lower levels of norepinephrine in both tumor and ascites at the time of surgery [12]. Norepinephrine is a hormone that is associated with the body's "fight or flight" response and is a product of stress. Increases in norepinephrine are correlated with cancer progression and a reduction in the number of ovarian cancer cells killed [15]. Social attachment has also been correlated to the activation of oxytocin, which is a known inhibitor of tumor growth, whereas social isolation has been linked to faster tumor progression [12]. This evidence indicates that social attachment remains a significant predictor of survival and demonstrates a survival advantage [14]. Therefore, supportive resources that facilitate environments of social support, such as Hospitality Houses, play an essential role in the survivorship of patients.

18.1 Financial Burdens of Cancer Care

How do patients find Hospitality Houses? After speaking with doctors, patient navigators, and professionals within a patient's medical network of care, many patients will search for supportive resources online [16]. However, is this a good place to start? The answer is both yes and no. For instance, when patients are searching for housing, and they search the term "patient housing in Phoenix," arrays of resources pop up that are not related to patient housing. Instead, they see advertisements for apartments and hotels within the Phoenix area. The issues arise from the terminology. Industry professionals are aware that the accepted term for a patient lodging facility is "Hospitality House," yet for patients, this term is not always prevalent, nor is it innate when searching for housing. Even though the accepted term is "Hospitality House," if one conducts an Internet search for the term, arrays of links pop up for

homeless shelters. This indicates that the term itself has not been branded enough for mainstream acceptance. Because there is an issue with the terminology, many patients do not discover the supportive environments found in Hospitality Houses, which results in them paying for apartments or hotels, unaware of other options. When calculating the short- and long-term cost of housing options along with the financial burdens of medical bills and a possible reduction in income due to illness, it becomes clear that affordable housing is essential for cancer patients.

The following letter was submitted to Editha House by a caregiver who stayed with us. He outlines how he learned about Editha House and his family's experience as a result.

My Son's Journey

In March of 2012, my son, Mathew, went into the hospital complaining of stomach flu-like symptoms that would not go away. Diagnosed with acute myeloid leukemia, he was transferred to Good Samaritan Hospital in Phoenix and received chemotherapy for the next 9 months. At first, Matt's wife Sarah and I shared the care of the kids at home and stayed in hotels in Phoenix. In 3 months, we had gone through over $8,000 in savings on hotel rooms and restaurants. We shared this information with the hospital, and it was then that we heard about Editha House.

While Editha House saved us financially, it also provided our family with a home during a very difficult period. Sarah and I were able to stay with Matt in a normal environment that was appropriate for his medical condition with loving staff members who clearly cared for Matt and us as people. Even though Editha House does not provide medical care, the staff understood not only the medical nuances of Matt's condition but also the broader issues affecting us as family members. To be able to prepare his own meals, watch football in the community living room, have others in similar circumstances to talk to, and feel like he was participating in his own recovery made an enormous difference to Mathew.

I am happy to say that Mathew entered remission in late 2012, and Matt and Sarah purchased their first home in January 2013. In late August, Matt returned to college to finish his firefighting and EMT training intending to return to work in September 2014. He has returned to his precancer 175 pounds and is extremely fit and energetic. All of us are extremely grateful for Editha House and are convinced that your facility made a significant contribution to Matt and our family's recovery.

Approximately one-third of cancer survivors in the United States report cancer-related financial problems [17]. These problems are correlated with an increased likelihood of forgoing or delaying medical care [8, 17, 18]. Because cancer diagnosis is associated with a reduction in income, due to fewer hours worked and an increased number of missed work days [19], having the additional burden of expensive cancer costs contributes to the stress of cancer patients, which in turn directly affects their quality of life and survivorship rates. During 2008–2010, the annual excess economic burden of cancer survivorship among recently diagnosed cancer

survivors was $16,213 per survivor age 18–64 years and $16,441 per survivor age ≥65 years [9]. Among previously diagnosed cancer survivors, the annual excess burden was $4,427 per survivor age 18–64 and $4,519 per survivor age ≥65 years [9]. These costs comprise the largest economic burdens among cancer survivors, especially for those recently diagnosed. Furthermore, these numbers do not take into account the additional financial losses experienced by caregivers as well as intangible costs associated with pain and suffering [9]. Lastly, these numbers do not reflect the financial burdens associated with the need to travel and cost of transportation to and from treatment facilities.

According to the President's Cancer Panel, lack of health insurance causes people to delay or even forgo cancer and other health care due to cost, often resulting in later stage of disease at diagnosis and shorter survival compared with insured individuals [8]. In addition to the poor being at the highest risk, the working poor and middle classes who do not have significant assets and are dependent on earned income are also susceptible to loss of income and employment [8]. Certain patient populations are at much greater risk for financial burden; therefore, healthcare providers must identify them as soon as possible and link them with the necessary services early in the disease process [9].

Fortunately, there are resources such as Editha House that provide affordable lodging for patients travelling for treatment. This aspect of supportive care has been shown to positively affect both the adaptation and survival time of patients relocating for cancer treatment [1]. In addition, having supportive care resources such as Editha House significantly reduces the financial burden of patients while providing an essential environment of compassionate care. Furthermore, a 2006 national study of households affected by cancer found that uninsured individuals with cancer were two to six times more likely to experience financial problems due to the cost of cancer care compared to insured patients [8]. These problems included depleting all or most of their savings, borrowing money from relatives, being contacted by collection agencies, seeking help from charity or public assistance, taking out loans or second mortgages, being unable to pay for basic necessities like food or heat, and declaring bankruptcy [8].

The number of cancer survivors in the United States is estimated to reach 18 million by 2022 [10]. Reducing their financial burdens by providing supportive care resources will continue to be crucial to their quality of life and survivorship. The financial burden that cancer has on families can be substantial, including lost income, increased insurance premiums, deductibles, co-payments, transportation costs, and childcare expenses [9]. The fear of losing employment (and therefore losing medical insurance) is also a factor that contributes to the stress of many patients [20]. Yet, even insured patients undergoing cancer treatment and seeking co-payment assistance experience considerable financial burden. The out-of-pocket expenses are sometimes unmanageable, and many patients may amend their treatment plans to defray out-of-pocket expenses because health insurance does not eliminate financial distress or health disparities among cancer patients [18]. Furthermore, experiencing financial distress or "financial toxicity" can be considered analogous to health symptoms associated with "physical toxicity" [18]. Patients

impacted by increased financial stress may experience more pain and more physical symptoms of illness, while patients with less of a financial burden may be able to focus more on healing.

18.2 Does Environment Matter?

When environmental stability is lost, it is essential that people act to re-stabilize themselves in the world surrounding them. According to the Institute of Medicine, over the past two decades, the 5-year survival rate for the 15 most common cancers has increased from 43 to 64 % for men and from 57 to 64 % for women [21]. Research findings have identified ways of improving the quality of cancer care and the health of patients. A growing body of scientific evidence demonstrates that psychosocial problems created or exacerbated by cancer, such as depression or a lack of information or necessary skills for managing illness, can be effectively addressed by a number of services and interventions [22]. Services that facilitate transportation or provide financial assistance are key resources to help support cancer patients and their families. Together, these services reduce patients' suffering, help them adhere to prescribed treatments, and support their return to health [21]. Hospitality Houses play a crucial role in the process of providing guests with a safe and comfortable environment while undergoing medical treatment and much more: Hospitality Houses provide guests with homes that actually feel like *home*.

18.3 What Is the Difference between a Hospitality House and a Hotel?

Accommodations are the most often overlooked factor that deeply influences a patient's quality of life during treatment [23]. The questions "Where are we staying tonight?" "What are we eating tonight?" and "How are we going to get there?" may seem trivial when the bulk of the time, energy, and money are spent on the illness itself; however, food, lodging, and transportation are the ever-present real-life issues. If left disregarded, they can lead to an overwhelming emotional and financial burden for the entire family, not just the patient diagnosed with cancer.

In order to increase a patient's quality of life, the first and most significant area of need is the patient's *practical* needs. These are the necessities that humans need to survive, such as shelter and food. However, the word "shelter" may not necessarily evoke images of a *home*; instead, many associate "shelter" with exterior structures, while associating *home* with interior elements such as the *feeling* within the house that makes it a *home*. Research from the Center for Health Design has shown that the more attractive the environment, the lower the anxiety level of the patients [24, 25]. When considering the difference between a hotel and Hospitality House, research indicates that having strong access to social support can reduce stress and having effective communication with knowledgeable staff can reduce anxiety, thus

improving the overall outcomes for the patient and family [14, 23]. In addition, having access to nature has been correlated to better quality of life, which supports positive patient outcomes as demonstrated through a reduction in stress and promotion of recovery [14, 24]. For patients with limited mobility, even having a view of a garden has been shown to have positive effects on health [13, 14].

Hospitality Houses provide guests with much more than shelter; they provide patients with a home to live in while undergoing treatment and foster a positive atmosphere of supportive care. The patients and their caregivers—the guests of the Hospitality Houses—can find solace in their environment and support from other guests in similar situations. A recent guest states it best when explaining how Editha House allowed him to access and receive treatment:

> *I was homeless and diagnosed with advanced laryngeal cancer. I had incredibly limited social security income and could no longer afford to live in a hotel. Every day I felt worse and I could barely speak. My treatment was going to take at least two months. I was extremely depressed. I didn't have contact with my family for many years. I felt alone and forgotten, and I was ready to give up completely. It was then that I was referred to Editha House. I remember being welcomed by the staff and feeling comforted and dignified for the first time in years. Not having to worry about how I was going to get through each day tremendously decreased my stress levels. The staff understood that I was limited in my ability to communicate because of my cancer. They anticipated my needs, and I will never forget what they did for me.*

This patient's experience is all too familiar. Facing the decision to undergo treatment is painful enough, but dealing with the additional burden of finances exacerbates the situation. Understanding that having access to an affordable home that *feels like home* is critical.

Another guest of Editha House—Raymond—from the Navajo Nation underwent treatment for pancreatic cancer, describing his experience while staying at Editha House as "an atmosphere of calmness and hope," adding "there is a natural ease about Editha House that is felt throughout the walls." His description identifies his perception of the general atmosphere. Unfortunately, he was placed in a similar position as many other guests that visit Hospitality Houses across the nation: if Raymond could not find an affordable place to stay, he would have had to forgo his treatment.

To date, guests from 42 states and 11 countries have made Editha House in Phoenix, Arizona, their temporary home with an average stay of 21 days. Hotel accommodations are extremely expensive, and moreover, they do not include the supportive community environment that is essential for patients. In fact, staying at a hotel for 21 days costs an average of $2100 during the off-peak seasons. Even for patients who can afford to stay in hotels or apartments for the duration of their treatment, Hospitality Houses still serve as a better option because they provide the psychosocial and environmental support that is necessary for healing. The need for Hospitality Houses is vast and central. Simply put, patients must be able to get treatment, and many times, it is a draw between location and finding affordable accommodations [2]. Hospitality Houses make all the difference.

18.4 The Importance of Caregiver Support

Cancer diagnosis has a major impact on patients and their entire families [24, 26–29]. Some research indicates that it has a greater effect on family members than patients because of the unexpected responsibilities and the compound difficulties in coping with the demands of the role [26]. In contrast to professional caregivers such as physicians and nurses, informal (or familial) caregivers are frequently family and friends who provide care for cancer patients. They take time off of work and do not receive compensation. They are concerned with disease progression and treatment outcomes, while working with the practical demands of care [29]. Often caregivers prioritize patients' needs over their own and therefore lose focus on their own self-care, resulting in diminished quality of life [30].

Studies have shown that the emotional and physical experiences involved in caregiving can strain even the most capable caregivers [28, 30]. The most common issues that caregivers face are physical, psychosocial, and economic [26]. Their responsibilities vary and range from handling personal care, mobility, transportation, housework, emotional support, administration of medications, managing the scheduling of medical appointments, managing money, meal preparation, shopping, to running errands [26–28, 30]. Many caregivers spend countless hours caring for their loved ones, and studies point to a prevalence of depression in caregivers of patients with advanced cancer [27]. Furthermore, research indicates that 40 % of spousal caregivers reported depressive symptoms that were considered clinically significant at double the rate of their ill partners [27]. Adequate social support is essential to caregiver success because it improves their quality of life and the quality of life of patients [26, 27, 29, 30].

Hospitality Houses tie into the reduction of caregiver stress by providing them with an environment of supportive care. In contrast to the isolation that may be found in hotels, caregivers can find and meet other caregivers who are in similar situations. Providing support for caregivers not only relieves their stress but also can have positive effects on the patients [26, 27, 29]. Many times, patients feel relieved to see their caregivers well-rested, showered, and fed. It reduces patient anxiety regarding the burdens of their caregivers and thus allows them to focus on their own healing.

A Letter to Editha House

July, 2014

Dear Editha House,

You will never know how grateful I am that you opened your doors and your heart to my husband and me. My life with cancer began in January 2014 when Jim was diagnosed with advanced pancreatic cancer. The world as I knew it shattered into a million pieces. I knew I had to find the best medical care I could, but I was given little hope here at home in Albany, NY. Through what I believe was divine intervention, I discovered a doctor in Arizona who specialized in the treatment of advanced pancreatic cancer with promising results. I felt that he would be our best choice. I felt there was hope at last…

and so our journey began. Two one-way tickets. Two hearts full of hope and lots of prayers.

Jim was accepted in a clinical trial. Treatment began. There was nothing I could do but care for Jim. It soon became apparent that living and caring for Jim in a hotel setting would have many challenges. Jim was getting chemotherapy and his immune system was severely challenged.

We were told to avoid crowded places due to the risk of infection. I met with a dietitian who gave me nutritional guidelines for cancer patients. How was I to give Jim the best care I could if we had to deal with all of the other guests, maids, restaurant crowds, and restaurant food preparation that I had no control of? Even with the medical discount the hotel gave us, the cost of staying there was quite expensive, and I knew that we would be in Arizona for a long time.

So here I was, in Arizona, thousands of miles away from my family and friends. My husband had advanced-stage pancreatic cancer. I felt alone and isolated. I was scared. My stress level was rising. How could the well-meaning friendly front desk person at the hotel know the gravity of his words when he looked up at me, smiled, and said, "Have a great day!"

I had a conversation with our patient care coordinator and told her of my many concerns about living in a hotel. She told me about Editha House. She said that Editha House was a Hospitality House for adult cancer patients and their caregivers. She said that it offered small apartments with private kitchens, and it was also was a controlled environment for the safety of patients on chemotherapy with compromised immune systems. My prayers were answered. I didn't know what a Hospitality House was, but I do now!

In February, we arrived at Editha House and were warmly welcomed. We felt at home immediately. I could finally follow Jim's treatment plan by cooking meals with his special needs in mind. I was told that the fees to stay at Editha House was just a suggestion and that you could pay the suggested price per night, which was surprisingly low, or if you couldn't afford it, pay nothing. It is the mission of Editha House to help lessen the financial burden of their guests so they could focus on their medical treatment and emotional well-being. You have allowed us to do that and we are so grateful.

You even told us to put our money towards plane fare, so we could travel to New York to be in our home with family and friends. If we were still living at the hotel, we would never have been able to visit home, as we have been able to. I don't know what the future has in store for us and these visits may well be very precious indeed.

The guests at Editha House are all from different places. All have a different story. All are fighting a battle against cancer of some form, but we share a special bond. We look at each other and there is an unspoken knowledge that we are on the same journey together, sharing the same ups and downs. When Jim lost his hair I told him not to worry that half of the house looked just like him. The patients are the main focus, and rightly so, but we caregivers have our own set of ups and downs. I have found so much comfort at Editha House. Where the staff asks me, "How are you today?" "How do you feel?" and "Is there anything

I can do for you?" I am so grateful for the staff's consideration. They will never know how much a smile, a kind word, and someone to talk to means when you are carrying the weight of caring for your spouse while trying to be strong and cheerful while you are actually tired, scared, and your heart is slowly breaking.

Thank you Editha House very kindly for all you have done for Jim and me. You are a little piece of heaven here on earth. I don't know what I would have done without you. I will be forever grateful for your kind and compassionate hospitality. The world is a better place because of you.

The need for Hospitality Houses is vast and central. Patients, caregivers, doctors, nurses, treatment facilities, and hospitals benefit from the impact of Hospitality Houses because they improve patient quality of life, which in turn can result in better health outcomes and patient satisfaction. When Mary Gauwitz, President and CEO of the Kapoor Foundations, met with the CEOs of multiple hospitals in Arizona, the number one need that was identified repeatedly was the need for patient housing. Each hospital's CEO expressed concern that some patients and caregivers were sleeping in their cars and RVs in order to avoid travelling great distances, while others were forgoing treatment altogether. They expressed that many times patients are required to receive multiple treatments that vary in duration, and many patients are required to stay within close distance to their treatment facilities. With the goal of improving cancer care, Editha House was developed in response to the great need expressed by these hospitals.

The healing environments found at Editha House and other Hospitality Houses across the nation have proven to be highly cost-effective for hospitals. They promote reduced length of stay with stronger recovery times, reduced readmissions, and better overall quality of care. The physical environments that patients experience are directly linked to how quickly they recover and how quickly they are able to adapt to their treatment plans [31]. With Healthcare Reform, there is a rise in hospital accountability regarding patient and caregiver experience. The self-reported questionnaires, that many hospitals provide patients and caregivers, are directly correlated to hospital funding. Patients and caregivers who have a strong network of care, which includes doctors, nurses, patient navigators, and staff at Hospitality Houses, may be more likely to experience and report positive outcomes. Research also indicates that these types of healing environments affect the amount of pain medications used, rate of hospital-acquired infections, cost of patient care, rate of provider satisfaction, and the heart rate, blood pressure, and respirations of patients [31]. These outcomes support the notion that more healthcare professionals and patients can benefit greatly from increased awareness of the impact of Hospitality Houses.

The burden of temporary relocation for treatment, paired with the shock of cancer diagnosis, is daunting. Hospitality Houses provide patients with a "home away from home," which allows them to focus on healing. Patients who are not aware of supportive care resources are at a significant disadvantage psychosocially and financially. These burdens directly connect to negative health outcomes for patients and caregivers alike. Raising the awareness of these facilities will benefit patients and

their families and will also directly benefit the cost-effectiveness of hospitals and the overall patient satisfaction reports linked to hospital funding. In the future, more attention and research should be conducted to investigate the impact of Hospitality Houses on patient outcomes to raise awareness and establish consistent branding for the term *Hospitality House*.

Table 18.1 National resources available for cancer patients and their families

Resource	Source	Description
Housing		
Editha House	www.edithahouse.org	Affordable, temporary housing for adult patients and caregivers in Phoenix, AZ
Healthcare Hospitality Network	www.hhnetwork.org	Nationwide association of nonprofit organizations that provide lodging and supportive services for patients and their families who are travelling to receive medical treatment away from their communities
IMD Guest House	www.imdguesthouse.org	Affordable, temporary housing for patients and their families in Chicago, IL
Joe's House	www.joeshouse.org	A lodging guide for patients
Ronald McDonald Charities	www.rmhc.org	Affordable, temporary housing for children and their families
Transportation		
Angel Flight Network	www.angelflight.com	Air transportation for medically compromised patients and their families
Angel Wheels	www.angelwheels.org	Ground transportation for medically compromised patients and their families
Corporate Angel Network	www.corpangelnetwork.org	Air transportation for medically compromised patients and their families
Caregiving		
Cancer.Net	www.cancer.net	Oncologist-approved cancer information
Caregiver Action	www.caregiveraction.org	Education, peer support, and resources for family caregivers
Caregiver Support	www.caregiversupport.org	General caregiving links and other information
National Cancer Institute (NCI)	www.cancer.gov	Comprehensive cancer information from the National Cancer Institute

*Check with your hospitality house and/or treatment facility to see if they provide transportation services or have a list of other transportation resources

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Supportive Care: The Patient's Perspective

19

Katya Lezin

19.1 My Cancer History (How My OB/GYN Fired Me)

My cancer journey begins with a pain in my rectum, which is ironic since I have often been described as a pain in that very same area of the body.

I first felt the pain in December of 2010, but it went away after a few days and I went back to my busy, no-time-to-see-a-doctor life. When it recurred a few months later, in April 2011, I could no longer ignore it. I called my OB/GYN, who squeezed me in during his lunch hour. An ultrasound revealed that one of my ovaries had torqued and twisted.

The word cancer never came up. Ovaries twist and descend for a variety of reasons, including excessive sex (a theory I rejected, noting that my husband would be astonished to learn that we were engaging in excessive sex) and excessive exercise (which made a lot more sense since I exercise to the extreme to try to stay on top of my equally excessive calorie consumption). The offending ovary was removed laparoscopically the very next day. I left for a conference in Philadelphia a few days later, which is where I was when I got the call from my doctor that we all dread getting, the one that starts with the words, "I don't know how to tell you this."

That call served as the demarcation between life as I knew it and my life as a cancer patient. The pathologist who examined my ovary (and how fortunate for me that all body parts that are removed are sent off for analysis pro forma) showed not only cancer but markings consistent with the BRCA genetic mutation. Genetic testing confirmed that I was positive for BRCA-1, which gave me an 85 % chance of getting breast cancer on top of the ovarian cancer I was already battling.

At first, it seemed a cruel twist of fate that I was alone on a business trip, away from my Charlotte, North Carolina, home and my husband and kids, when I received the devastating cancer diagnosis. But in retrospect, I have come to appreciate the

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opportunity this presented to process and absorb the news before facing my kids, who were 11 (Eliza), 15 (Hannah), and 17 (Noah) at the time. I had a few days to wrap my head around the fact that I had cancer and to go from shocked and numb to fighter mode. By the time I returned to Charlotte 2 days later, I was ready to reassure my kids, and everyone else, including myself, that I would beat this and emerge from the journey even stronger.

I met with my gynecological oncologist at the Blumenthal Cancer Center (now the Levine Cancer Institute) and learned that I would need a full hysterectomy. During that surgery, I would have a peritoneal port inserted in my abdomen so that my chemotherapy (Taxol and cisplatin) could be blasted directly to the site of the cancer. I also met with a breast surgeon and a plastic surgeon and elected to have a prophylactic double mastectomy, which was scheduled for mid-December.

I chose to have a DIEP (deep inferior epigastric artery perforator) flap procedure, in which the new breasts are formed by using one's own stomach fat (I even offered to make additional breasts for women who didn't have the good fortune of my excess fat), partly because I liked the idea of one surgery versus ongoing procedures with silicone implants and partly because I wanted everything to fall within 2011 for both financial (I had already met my insurance policy's catastrophic cap) and emotional reasons (I could start the new year afresh with no looming surgeries or procedures). Unfortunately, my plan backfired because I experienced unanticipated complications requiring multiple corrective surgeries and hospitalizations the following year… but I get an A for effort.

In October 2013, just a few weeks shy of making it to the 2-year milestone of being cancer-free following the conclusion of my chemotherapy, my cancer recurred. My CA 125, a blood marker that is a good prognosticator of ovarian cancer, had been steadily climbing. Sometimes, this occurs for innocuous reasons, like stress or a noncancerous infection, so my elevated CA 125 levels were not overly concerning, especially since CT scans revealed nothing out of the ordinary. But when my CA 125 was in the hundreds, a number that made it irrefutable my cancer had come back, a PET scan confirmed that it had recurred by revealing a tiny lesion on my spleen. I had a splenectomy in November 2013 and no further treatment was warranted because all visible signs of cancer were removed.

So for those keeping count, I was minding my own business, happily living a busy, engaging life one minute, and the next I embarked on a journey that has included seven surgeries, 5 months of chemotherapy, ten hospitalizations, the loss of my hair and multiple body parts, hundreds of needle pricks and stitches and indignities large and small, and the occasional fear that each milestone I enjoyed with my family would be my last. (Not to mention the humiliating moment when my OB/GYN, the same doctor who initially diagnosed my cancer, told me that there was no longer any need to see him because, as he put, "you've got nothing for me.")

But my cancer journey has also included many moments of levity and mirth, far more than I would ever have imagined. It has made someone who already

appreciated her life and all the people in it that much more aware of how very lucky I am, and it has strengthened and enhanced the bonds I share with my family and friends. There were many parts of my cancer journey that were just plain awful and I would never wish to embark on this journey or wish it for anyone else. But since none of us have a choice, in that we don't get to say, "No thanks, Cancer, I have other plans, pick someone else," we might as well face it and make the best out of it. And I am here to say that good can come out of the bad and that there can be light and joy and humor on a cancer ride.

I did not embark on this journey alone. There were certain things no one could do for me, certain blows that could not be softened, but even then I knew I had a veritable army of supporters by my side. And for everything else, from navigating the new and perplexing medical world to rides to the hospital to hats to wear atop my bald head to meals for my family and distractions for my kids, the support I received made my journey so much more bearable. It made the difference between just getting through it and being able to find the silver linings and the humor in it. I have come to realize that within the realm of unlucky, I have been extremely lucky.

My family rubbing my bald head for good luck in our holiday photo 2011, the year I was diagnosed with ovarian cancer

19.2 An Overnight PhD in Patient Expertise (Navigating the Medical World)

When my OB/GYN told me he'd be referring me to a gynecological oncologist, it sounded like he was speaking a foreign language. Many of the medical terms and even the names of the specialties that were bandied about in those bewildering few days when I was at my most vulnerable were challenging to pronounce and even more challenging to comprehend. It is easy to feel overwhelmed and alarmed by the breadth of one's ignorance, and getting up to speed on what is happening within your body and why and what your options are to combat this new foe can seem like an impossible task. It can also be emotionally daunting to learn about what is happening to you and what lies ahead, to get your head around mutations and poison seeping into your bloodstream and cells being destroyed.

But I am a firm believer in being a hands-on partner in this medical battle. Your doctors and medical team are not doing this *to* you, they are doing this *with* you. An informed patient is one who will know what should be happening and can therefore be on the lookout for things that have gone awry. An informed patient knows her own body and can report what is working and what symptoms need added attention. And an informed patient asks probing questions, seeks second opinions, and explores multiple options to ensure she is getting the best care possible. So here are my thoughts on how to be an informed patient, what to do and what not to do to secure not only the best outcome but also the smoothest journey.

First, whenever possible, take someone with you to your appointments. There is simply too much information coming at you in an abbreviated amount of time (most doctors run continuously behind schedule and do their best to be in the moment with you, but the reality is that there is a lot to cover and little time to do so) and too much going on. Your thoughts are racing and trying to process what was just said and now you've missed the next key piece of information. Having someone there with you ensures that two sets of ears are taking all of this in. My husband accompanied me to almost all of my major appointments and he took copious notes. These notes helped us review what we were told, compile questions about things we needed to better understand or about which we wanted to seek additional information, and sometimes only made sense to us weeks or months down the road, when a procedure or treatment was upon us and we could refer back to the notes describing it.

Be an engaged and active partner in your care. Tell your doctor things he should know about you. In an ideal world, our doctors would be able to sit with us for hours and learn about our fears and life goals, but that is not the reality of most medical appointments these days. So be proactive. I learned early on that nausea was my push-button issue. I have a pretty high tolerance for pain, but I have none for nausea. It impacts every aspect of my life because when the world is spinning, you have to lie down, and a bedridden Katya is a miserable Katya. I learned to advocate for myself, to alert my medical team that my nausea was intolerable and that I couldn't

do 5 months of it without going insane. They, in turn, made getting in front of my nausea a top priority. Each of my chemo sessions was followed by several days of intravenous antinausea drugs (a better course for me than ingesting them) and fluids to keep me hydrated. They would not have known to do this, to find a solution for a problem that was bringing me down, had I not advocated for myself and made sure it was on their radar.

Another way I advocated for myself was to let them know what an active, busy life I had. I let them know all of the plans I had for the summer – college visits with my son, out-of-town Scrabble tournaments, outings with my kids and husband – all of which I was loath to miss. I made it clear that my emotional well-being was inextricably linked with my physical well-being and that continuing to live my life as before was important to me. We made the joint decision, based on my need to maintain my busy schedule and to travel throughout the summer, to forego the clinical trial for which I was qualified because that would have required me to stay put in Charlotte for the whole summer. I needed the flexibility of scheduling my chemotherapy around my schedule rather than being bound by a clinical trial's strict regimen of care. This was the best decision for me, but it was only reached because I shared important information about myself and my medical team took that into account when laying out my options and advising me what to do.

And no matter how renowned and fabulous your doctor and medical team may be, it is always helpful to get a second opinion. Let me revise that, since I am being hypocritical given that I didn't officially seek a second opinion for myself. I am blessed to have a slew of doctors as relatives and friends, so my second opinions came frequently – often solicited but sometimes unsolicited – and I did not feel the need to seek a formal second opinion. I do think it is important to ensure that you have as much information as possible – from more than one source – when making crucial decisions about your medical care. A doctor who is secure in her professionalism and expertise should not resist your seeking a second opinion. I would be wary of any doctor who doesn't want you to question what she says or seek confirmation of her diagnosis or plan of attack.

Sometimes, even when we do a masterful job of advocating for ourselves, things do not work out as planned. When my cancer recurred, and I faced my seventh surgery, I explained to my new surgeon (who specialized in splenectomies, which is why my oncologist referred me to him) that I had suffered a mysterious rash and infection or allergy (the source of the rash baffled my entire medical team) following each of my last three surgeries. I had also been hospitalized with a postsurgical infection a full 3 months after my mastectomy that had required a 5-day stay in the hospital and had almost killed me. I told him that I did not want to leave the hospital before we were sure that the rash was gone for good, because I had returned via the emergency room several times, and we all agreed that it was best to avoid letting things get to that point. When my body responded to the splenectomy the way it had for my previous surgeries, my new doctor prescribed antibiotics. The rash went away and he came by to discharge me.

"But it tends to come back after a day or two," I explained, frustrated because I had already handed him, on a platter, my one concern about my surgery when I'd met with him in our initial consultation.

"Go home," he said patronizingly, patting my stomach (the same one that had just experienced a major surgery). "It'll resolve itself."

I ended up calling in some of my friends who are doctors on staff at the same hospital, and they, in turn, called in an infectious disease specialist who agreed that I should stay an extra day or two to ensure that the second type of antibiotic (because the rash had, as predicted, flared up again after the first antibiotic) did the trick.

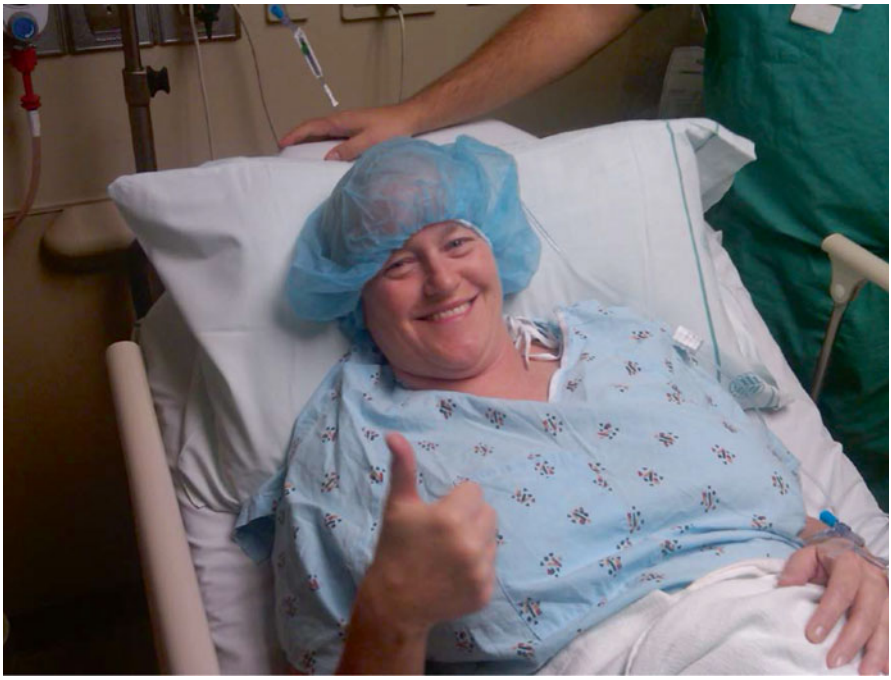
That experience marks the only time in my entire cancer journey that prompted me to write a letter of complaint. The irony is that my clinical outcome was great. I had the surgery on a Friday, I was released on a Tuesday evening, and I was working out at the gym the next morning. This surgeon's skills are considerable. But those skills cannot exist in a vacuum. I did not feel heard, and that is the death knell of the doctor-patient relationship. Only treating my spleen, and ignoring the heart and brain that are attached to that spleen, makes for bad medical care. If this happens to you, stand up for yourself. Make sure that your concerns and questions are addressed. You deserve no less. (I now share my experience with groups of doctors, residents, and medical students in large part because I know that there are many more marginalized patients out there who do not have the resources I did to rectify the situation.)

We now live in a time where much of the information that was once only available in medical school is now readily accessible to all of us on the Internet.

I caution you to proceed carefully with these floodgates of information. The good news is that there is a wealth of information out there about every type of cancer. The bad news is that not all of the information is correct or appropriate for you to see. I made a conscious decision to limit my access to the Internet as a resource for learning about ovarian cancer. Frankly, what little I saw was downright depressing. I opted instead to focus on the positives and use the Internet to research specific treatment options or side effects I was experiencing.

When my neuropathy (a nerve sensitivity that is a common by-product of chemotherapy) reared its ugly head a full 8 months after my treatment was finished, I was flummoxed and beyond frustrated. Visiting websites that shared home remedies for combatting the annoying tingling and reading about women who had it way worse than I did (always a good remedy in that it gives you perspective and stops any pity party in its tracks) proved helpful.

Each patient will have to navigate what works best for her in terms of staying informed and playing an active role in her care. For me, my doctor friends and relatives proved invaluable in translating impenetrable *medicalese* and helping me weigh my options. For others, it may be a cancer support group or a chemo navigator or a particularly informative and accurate website. The source of the information is not as important as the information itself. Stay informed, if for no other reason than it allows you to regain some of the control that was taken from you when the Big C first rocked your world.



On my way to my double mastectomy in December 2011. Nothing says "I feel vulnerable" more than a hospital gurney and the prospect of major surgery

19.3 At Least I'll Lose Some Weight… Not (Managing Your Physical Symptoms)

I am almost embarrassed to admit this, because it makes me seem so shallow, but one of my first thoughts after learning I had cancer was that at least I would finally lose some of my unwanted pounds. My antiquated view of cancer conjured up emaciated women who couldn't keep anything down. I figured that would be a silver lining, but that was definitely not the case for me. I had no appetite on my chemo days, but I more than made up for it on other days. I was getting a heavy dose of steroids to help with my nausea and other symptoms, and I was also thrust into menopause overnight thanks to my hysterectomy. I actually put *on* weight during cancer, and I know I am not alone.

In a cruel twist of fate, I simultaneously battled horrible nausea while steadily gaining weight during chemo. On both fronts, I found it extremely helpful to talk to my cancer center's dietician. She was well versed in dietary dos and don'ts but also knew the nuances that were unique to cancer patients and to my cancer in particular. I also found it helpful to talk to my nurse practitioner about my symptoms, because she could often explain them or put them in context, which

somehow made them more bearable. When I suddenly developed a metallic taste in my mouth, I learned that it was the cisplatin peaking in my body 10 days after it had been administered. When it hurt to eat and drink toward the end of my chemotherapy, I discovered mouth sores and knowing they were temporary helped immensely.

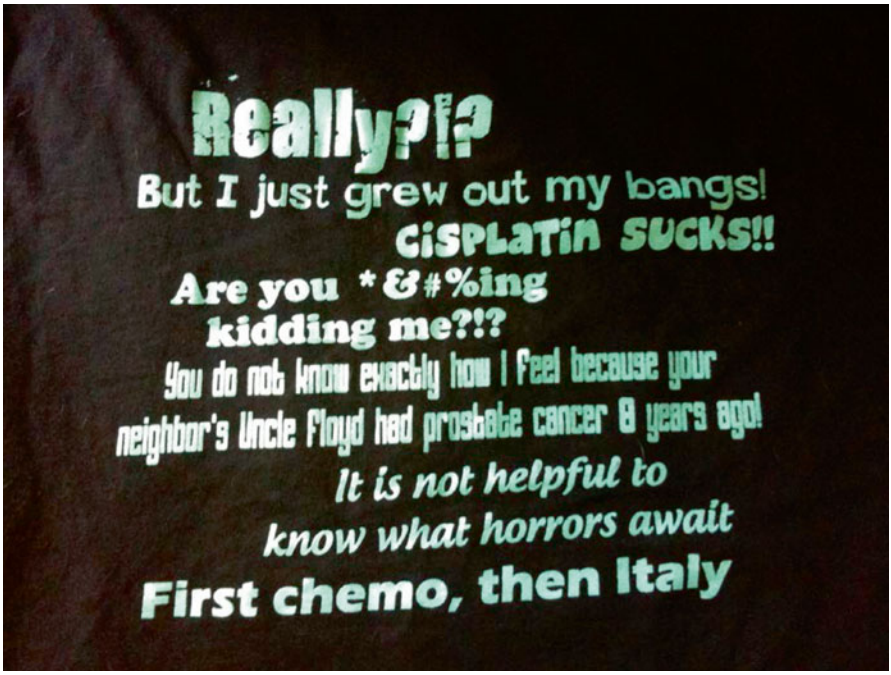
Another great resource are fellow patients or, better yet, those who have gone through your surgery or procedure or chemo regimen and are now able to reflect back on what worked and what didn't and what they wish they had known. But the caveat is that the advice and insight have to be solicited. Some people seem to delight in telling you, in excruciating detail, all of the horrors that await you. If you've asked for it, and want an honest accounting of how hard it was, great. Go for it. But the more likely scenario is that you want just enough to prepare yourself or any tips that will help you avoid certain pitfalls. Beyond that, folks should keep it to themselves.

I am often asked to reach out to someone's friend or colleague who has recently been diagnosed with cancer. I freely give out my contact information, suggesting that the person reach out to me rather than the other way around. Every journey is different and everyone has a different way of coping. No one way is better than another. (Okay, if your coping mechanism is to shoot heroin, then I think we can safely say that is a bad coping mechanism.) I chose to forego scarves and hats and instead paraded around town in all my bald glory. One of my friends wanted me to convince her neighbor to do the same. I declined. We each have to find what feels comfortable and right for us, and no one else can tell you what that is.

But whatever you decide, and whatever route you choose to take, whether it's a certain kind of treatment or a particular doctor or whether to have prophylactic surgery (as I did with my double mastectomy), surround yourself with supportive people. Anyone who second guesses you or makes you feel bad about your decisions needs to be reminded that she is not the one fighting this battle. You are, and you have to live with the decisions so they are yours to make.

At the risk of coming across as a total hypocrite, now that I've said advice should only be given when solicited, I will say what worked for me in the hope that it serves as an encouragement for anyone who feels she has to ride this out in seclusion. My greatest source of strength was the love and support I received from those around me. I sent out regular emails to friends and family near and far, with *Ovarian Odyssey* in the subject line, and the cyber support I received back always lifted my spirits and often provided just what I needed to get through a difficult time. Don't try to do this alone. It is too hard. Let others get in the ring and fight with you.

Running the Race for the Cure with a bunch of my friends, who had shirts made with some of my favorite cancerisms printed on the back



The shirts my friends and I wore with things I had shared in my Ovarian Odyssey emails about my cancer journey

19.4 You Are Being the Opposite of Helpful Right Now (Setting Boundaries with Friends and Family)

One day, around the midpoint of my 5-month chemo cycle, I dragged myself to the gym. I felt lousy, but I concluded that I could feel lousy lying in bed or I could feel lousy on the elliptical. I figured I might as well work out and get some endorphins going. I was slowly making my way across the parking lot, feeling as if it were on an angle and finding it hard to stay upright, when an acquaintance waved me down. I didn't feel like talking to anyone, but I assumed she wanted to see how I was doing and to wish me well and the least I could do was thank her for her concern and let her know how much I valued all of the support I had been receiving.

I was wrong. This acquaintance was upset. She was ranting before we'd even reached each other.

"I was on your meal plan long before Susan signed up," she complained. "But I have been kicked off of it and Susan, who signed up after I did, is still on it."

I just looked at her, dumbfounded.

"I tried to sign up again and it's *full*," she said, accusingly. "It's not fair."

I kid you not. This person, who was supposedly trying to help me during my time of need, was lambasting me about how difficult it was to help me. I explained, using energy I would rather have devoted to working out, that the excess of meals was proving more stressful than helpful. David and the girls couldn't keep up with all of the food and my poor husband felt compelled to drive home from whatever activity the girls had on a particular night to heat up a meal that had been left for us, even though it would have been more convenient to just stop somewhere with them or eat the leftovers that were building up. So I had asked my friend Lorrina, who had set up the meal plan, to cancel some of the people on it.

"But I signed up ages ago," this determined meal giver responded.

I agreed that seemed unfair, when what I wanted to say, no *yell* at her, is, "THIS IS NOT ABOUT YOU."

You will find, as you navigate the sea of well-wishers that surround those of us who are fortunate to have so much support and assistance from friends and family, that not all of the gestures of love and support are well-intentioned. They may have started out that way, but they take a detour and become much more about the person making the gesture than the person receiving it. This sometimes took the form of cards I received with an overly religious message, that reflected what was comforting to the cardgiver much more than what made sense for me. Or the well-meaning but truly annoying advice I received about diet, rest, and any other aspect of living my life with cancer. Again, this is fine if I solicit opinions, as I often did, but not when it is just someone thinking she knows best.

I did several things that really helped me harness the support I wanted and needed and set boundaries with the unwanted and unsolicited help. The most helpful thing I did was appoint a couple of dear friends as point persons. One fielded requests for meals and other gestures, conferring with me on what I needed and then communicating it to everyone else, serving as a buffer between my family and the rest of the well-meaning world. My other friend set up a chemo buddy schedule, assigning people 2-h

shifts to visit me on my chemo days to ensure that all of the times I wanted company were covered and, perhaps more importantly, that I wasn't bombarded with visitors or exhausted with trying to appease everyone who wanted to come see me.

Don't get me wrong. Support is a wonderful thing. I felt so lucky to be surrounded by such dedicated and creative and generous friends and family. It definitely beats the alternative of not having anyone clamoring to do something, anything, to lighten your load and make your cancer journey more palatable. But stand up for yourself and your family. Set limits. Articulate what you need and what you don't.

We set up a cooler on our front steps so that folks who brought us dinner could just leave it in the cooler. That way, we didn't have to be home for the drop off and, even if we were home, we didn't have to socialize if we didn't feel up to it. We let good friends know that the most helpful thing they could do for us was reach out to our kids, keeping them occupied and distracted while I was hospitalized or incapacitated. And when I was asked what we really needed and wanted, I was honest and said that gift cards to restaurants we frequent would be most helpful. That way, we could pick something up en route to the hospital or eat on the road when trying to maintain the girls' busy schedule. Instead of demurring and saying, "Oh, that's so kind, but you don't need to do anything" or "Anything is fine," be honest. Folks who ask are going to do something for you regardless of what you answer, so you might as well help them make sure their lovely gesture is something you need and want.

With my sister, Nicole (on my left), and friends at one of the many meals and special outings that I came to refer to as my "cancer perks"

19.5 Who Knew Cancer Could Be So Funny? (Humor as a Coping Mechanism)

There are many parts of my cancer journey that were just plain awful. The unrelenting nausea, the trauma my body suffered from chemotherapy and surgeries, the loss of hair, body parts, and my faith that exercising and living a healthy lifestyle would somehow insulate me from the dreaded C. But none of that was unexpected. Anyone who has pondered any of the indignities that a catastrophic illness engenders imagines all of that and more.

What came as a surprise, and a most welcome and happy one, is how many moments of mirth and levity my cancer journey provided. I am not just talking about the silver linings – and there were plenty of those too – but rather the outright funny things that stemmed from this unique life event. Part of that is due to my own sense of humor and my eagerness to find what is joyful and amusing in what is happening to me and around me. But the humor of my cancer experience also came from those around me, who did their part to inject humor into their gifts and gestures and perspective, making much of my ride surprisingly amusing and enjoyable.

My sister, in particular, outdid herself with creative gifts that found the funny in what I was going through. She sent CANCER SUCKS water bottles for me and my friends when we ran in a Race for the Cure event. When I developed a metallic taste in my mouth, something that was actually quite upsetting to me because of my fear that my taste buds would be forever tainted, she sent a Metallica gift box, complete with practical gifts like a tongue scraper and butterscotch candies, but adorned with a picture of the heavy metal group Metallica. But by far, the funniest and most creative gift my sister made for me were my very own cancer cards, that say things like *Please do this for me. Why*? *Because I have cancer* and *I have cancer. You do not*. These cards were a huge hit with fellow patients, medical personnel, and random strangers alike. They let people know that mine was not a morose tale of woe. I was finding the funny, and that helped us all have a better outlook.

There were also some situations that didn't begin humorously but sure ended up that way. When I was getting my head shaved just after starting chemo, I did so at a swanky salon and took my girls with me to get pedicures so that the experience would be more celebratory than traumatic. When my hairdresser's next client came in for her appointment and was unable to hide her dismay at my closely shorn head, I said, conspiratorially, "Watch out. All I asked for was a little trim." Her look of horror as she was led away for her own haircut had my girls giggling, and we all knew in that instant that it would be okay. Finding the humor let them know, and me as well, that the core of me remained intact. We were not in for months of doom and gloom. We could still find things to laugh about.

There will be much that is not funny. And those trying to find the humor in a cancer ride should take their cues from the patient. If I hadn't had a sense of humor about all that was happening to me, those gifts from my sister would have backfired. Every person has to find what works for her, and some situations do not lend themselves to laughter. But I do think many fall in that nebulous category that can go either way, and some are so bad that they actually become funny in the new low they establish. My advice is to find the funny; it makes the ride so much more enjoyable. When given the choice, choose to laugh instead of cry.

My daughter's suggestion for what I should have tattooed onto my new breasts instead of nipples

19.6 The Silver Linings (The Good That Can Come out of the Bad)

I often told my three children, when they were young, that it is easy to be good at Disneyland. The real trick is behaving well when things aren't going your way. Along those lines, I always knew I had a good marriage, but I also knew that we'd never really been tested. Cancer allowed me to see how strong my marriage and my children are and it strengthened our family unit in immeasurable ways. I have always appreciated my friends and family, but cancer let me see many of them in a new light, and it made me appreciate them all the more. And this newfound appreciation of how good people are, how kind and generous and supportive they are, was not limited to my inner circle. Neighbors and acquaintances and even strangers would blow me away with their gestures big and small and their compassion and generosity.

I also found that the cliché about no longer sweating the small stuff really does apply when you have faced your own mortality. The arthritis I have developed in my knee following a recurrence of my cancer has slowed me down to an annoying degree, but I remind myself that I am lucky to be facing an ailment of old age. Bring on the old age aches and pains because they beat the alternative. I am still here.

Many of the silver linings of my cancer journey would not immediately appear to be signs of good fortune. Sometimes, you have to actively seek them out or develop a mind-set that allows you to see the good within the bad. When I lost my hair, I enjoyed the low-maintenance bald do and when my hair grew back, I delighted in the thick curls that were a welcome change from my straight, fine hair. My double mastectomy was traumatic, to be sure, but it also came with a free tummy tuck, and I am now able to go braless. And when my cancer recurred, something I had feared and dreaded, I was able to appreciate the stroke of good luck within the bad. The lesion was able to be taken out in a single surgery, requiring no further treatment, and of all the organs to pick for a recurrence, a spleen was probably my best option.

I was fully cognizant of how fortunate I was to have such a strong support system throughout my cancer journey. My friends rallied around me, my husband and kids reminded me every day how strong and brave and beautiful I was, and my parents and siblings and extended family helped us financially, sent cards and gifts, and made sure we knew that we had a veritable army behind us.

My visits to the infusion room were constant reminders of how lucky I was, because I would often encounter people who had it so much worse than I did. I remember one woman commenting on how nice the air conditioning felt in the hospital because she didn't have any in her apartment, or another woman who apologized for being late but one of the two public buses she had to take across town to get to the hospital did not show up on time. And there were so many people who would spend the day alone, with no one to comfort or distract them while poison seeped into their veins. My constant stream of visitors, bringing me fuzzy socks and magazines and food aplenty along with companionship and compassion, made me feel like I had such an embarrassment of riches.

When my chemo was over, I resolved to do something about this disparity. There is so much that cannot be fixed or ameliorated, but this was something that seemed relatively easy to address. I approached my hospital's administration about starting a chemo buddy program, and they cut through all of the bureaucracy and red tape that usually bogs down such initiatives and made it a reality within a few months. Now, chemo patients at Charlotte's Levine Cancer Institute can self-identify as wanting a buddy, and the trained volunteers who are on shift that day will sit with them and provide whatever companionship is wanted and needed.

I have chronicled my cancer journey in *The Charlotte Observer* and in a book I wrote about my experience, *But I Just Grew Out My Bangs*, *A Cancer Tale*. I speak to cancer support and advocacy groups and to groups of doctors, residents, and medical students about my experience as a patient. I relish the opportunity to talk about ways of making the cancer journey better, for patients in terms of their own outlooks and approaches to their illness and treatment and to medical professionals in terms of improving the patient experience. It makes me feel that what I went through was not in vain. My journey served a purpose.

There was plenty to laugh about during my cancer journey, one that ended up yielding more good than bad

19.7 Supportive Care Toolbox

Every cancer journey is unique and each of us has to forge our own way once the Big C interrupts life as we know it. Now that I have had some time to reflect on my journey and what allowed me to not only survive but thrive, I have identified some of the coping mechanisms and tools that were most helpful in my overall battle and in the daily ups and downs, as well as those things that were decidedly unhelpful.

You will want to create your own toolbox and then play the cancer card to adhere to it. If people dropping by, no matter how well-meaning, depletes your energy and is not helpful to you, let them know. If you are reticent to ask for help but you need folks to walk your dog, identify the need to accept help and to reach out for favors and assistance in your toolbox.

A catastrophic illness is an amazing opportunity to be truly honest with yourself and others about what is important to you and what works and what doesn't. Creating a toolbox can help you eliminate the emotional clutter that surrounds any illness and life interruption and will allow you to identify those things that truly matter to you and are effective tools during this difficult time, and perhaps moving forward as well.

Here is what I recommend keeping on hand during your journey:

- Supportive and caring family and friends who respect your boundaries and needs.
- A sense of humor.
- Information tailored to your medical needs, allowing you to be proactive about your care.
- A medical team who guides and supports you, respecting the partnership you have together in your care.
- Your sense of self. No matter what is done to you and how much you change physically, the core of you can and will remain intact.

It is equally important to identify what doesn't work for you and to share these limitations and push-button issues with others, when relevant. This is a time when you get to be selfish. Focus on you and what makes *you* feel better. Here is what I recommend discarding:

- Friends and families who project their needs rather than addressing your own.
- Extraneous and alarming information – beware the Internet!
- Medical personnel who marginalize you and do not respect your role in your care.
- Angst about your precancer life. Enjoy the fact that you are still here to appreciate life postcancer.

Erratum to: Palliative Care

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