Exercise Oncology

Prescribing Physical Activity Before and After a Cancer Diagnosis

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To Sara, Mack, and Tom.

Preface

In 2018, the American College of Sports Medicine held the Second International, Multidisciplinary Roundtable on Exercise for Cancer Prevention and Control. During this 2-day meeting, attended by 39 international, multidisciplinary leaders in the field of exercise oncology, the most up-to-date science in the field was presented. Over the months that followed, as the three papers from the roundtable began to take shape, it became clear that many important insights shared at the roundtable meeting would not make it into the three papers. Around this time, Springer contacted me and asked if I would be interested in editing a book, on a topic related to exercise oncology. I saw this as an opportunity to document the current state of the field and point toward the future as well. Most of the presenters at the meeting were able to accept the invitation to contribute a chapter to this volume. Where that was not possible, additional experts have been identified. I hope the book is useful to any and all who are interested in advancing the growing field of exercise oncology.

Hershey, PA, USA — Kathryn H. Schmitz

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Chapter 1
Exercise Oncology: The Past and Present

Kathryn H. Schmitz

The historic roots of exercise as medicine reach as far back as 600 BCE. An Indian physician, Sushruta, is said to have been the first to have prescribed exercise for health [1]. He referred patients to exercise because "it made the body stout, strong, firm, compact, and light, enhanced the growth of limbs and muscles, improved digestion and complexion, prevented laziness, and reduced senility" [2]. The better known quote from antiquity regarding exercise and health comes from Hippocrates, from 460 to 370 BCE, who said "eating alone will not keep a man well, he must also take exercise" [1]. Since that time, our understanding of the health benefits of exercise has grown tremendously.

References to cancer date even further back in history. The oldest references to cancer appear to be from the Edwin Smith Papyrus documents from Egypt, dated 3000 BCE, which describe a bulging tumor of the breast "grave, for which there was no treatment" [3]. The oldest treatment for cancer appears to be surgery, though some dietary and topical treatments are described in early medical texts [3–5]. The assumed causes of cancer prior to cell theory precluded much effort in the direction of prevention, so there does not seem to be much attention to prevention until multiple millennia later.

To our knowledge, the first written work on the topic of cancer prevention came in 1761 when J Hill of London described a connection between tobacco use and several types of cancer [5]. Though the beneficial effects of exercise in the context of health have been understood for millennia, it was not until recent history that exercise was studied in the context of cancer prevention, treatment, and survival. Below we review this history specifically for the areas of epidemiology (primary and secondary prevention), preclinical models (mechanisms), and clinical trials in patients with a cancer diagnosis, as a backdrop to the advances described in the chapters that follow.

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Epidemiology (Primary and Secondary Prevention)

The first mention of exercise in cancer-related epidemiologic research might be from Ewing in 1911 [6]. In reviewing the forward public health progress from implementation of sanitary measures, he concluded that improved sanitation did not affect cancer incidence. He noted that the poor did not develop cancer, which tended to victimize wealthy individuals. The implications of this observation, related to what we now call "energy balance," are discussed in detail in Chap. 15.

In 1921, Siversten and Dahlstrom [7] reviewed over 86,000 death certificates and compared causes of death to occupation. They observed that the likelihood of dying of cancer was inversely associated with the amount of muscular work associated with the occupation of the deceased. The authors conclude that the increase in cancer was the result of less activity in the "age of machinery," what we now call the industrial revolution. Remarkably, Siversten and Dahlstrom noted: "Human carcinoma may be the reaction to and result of chronic irritation of adult epithelial tissue bathed in body fluids altered by certain metabolic products as a result of deficient muscular activity." This prescient observation is consistent with recent evidence presented in Chap. 4 of this volume.

FL Hoffman published a textbook in 1937 [8] which included results from a retrospective cohort study of 4000 adults (2234 cancer patients, 1149 controls). Based on "a lengthy questionnaire," Hoffman concluded that the nutritional intake of cancer patients tended to be excessive. "…Excess nutrition demanded an outlet in physical activity which is rarely met with in modern life." Hoffman felt that the latent power of growth and development likely found an outlet in cell proliferation. Again, the theme appears to be the potential for exercise to have its effects on the prevention of cancer through the mechanism of energy balance, as described in Chap. 15.

In 1984, Garabrant, Peters, Mack, and Bernstein [9] published the first of what has become a field of epidemiologic studies on the relationship between physical activity and colon cancer. A retrospective cohort study of 2950 California men documented that risk of colon cancer was 1.6-fold higher among those with sedentary jobs, as compared to men with the most active occupations.

In the decades since these early studies, there has been a proliferation of observational research linking exercise to cancer prevention. As will be described in Chap. 2 of this volume, we now have compelling evidence that physical activity is associated with the decreased risk of colon, endometrial, breast, esophageal, liver, bladder, gastric, and renal cancers. Evidence is growing that there may also be a relationship between physical activity and decreased risk of pancreas, ovary, head and neck, prostate, and hematologic cancers. The role of excess sedentary time and an increased risk of cancer are also discussed in Chap. 2.

Research on the potential for exercise to alter outcomes *AFTER* a diagnosis of cancer began far after the observational research on exercise and primary cancer prevention. However, by 2019, 145 observational studies had been published that examined some aspect of the association between physical activity and

cancer-related mortality. The evidence that both pre- and post-diagnosis physical activity improve survival after cancer is reviewed in Chap. 3 of this volume.

Mechanisms (Preclinical Research)

The earliest reference to the influence of exercise or fitness in preclinical cancer research is from Bittner in 1935 [10], who observed that in altering the diet of mice, the age at which cancer would appear varied according to the physical condition (fitness) of the animal. In 1938 Siversten [11] repeated Bittner's experiment but added 2 hours of exercise to a random half of the animals. The rate of onset of carcinoma was 16% in the exercised mice, compared to 88% in the non-exercised mice. In addition, carcinomas tended to develop at an older age in the exercised mice. Thus, we have known that exercise training reduces the growth of tumors for more than 80 years. Vischer and Siversten et al. [12] conducted further caloric restriction studies in mice to better understand WHY these animals were less likely to develop cancer. They observed that the calorie-restricted animals exercised more than the animals fed ad libitum and concluded that the extra exercise, in combination with the caloric restriction, reduced the amount of carbohydrate and fat available for cell proliferation.

In 1944, Rusch and Kline [13] conducted multiple experiments relevant to exercise and cancer. The first established slower growth of a transplanted fibrosarcoma with exercise. The second was a trial that randomized mice to receive exercise or not, and within the exercise group, half received exercise on a constant basis (16 hours), while the other half did exercise and rest in alternating 2-hour bouts, with a similar total dose of exercise over 24 hours. Four weeks later, both exercise groups showed less cancer than the sedentary groups, with no differences according to the pattern of exercise.

In 1952, Rusch [13], at the famed Wistar Institute, used a model of exercise intended to induce stress (forced swimming) to evaluate the hypothesis that stress would actually increase the incidence of cancer in mice. Notably, Rusch demonstrated the opposite – swim training actually decreased the rate of death from cancer compared to sedentary mice. Dr. Rusch continued this line of inquiry, verifying results over a series of experiments and concluding that there may be some optimal dose of "stress" (exercise) that could protect from cancer. This may be the first reference to research on a "dose response" effect of exercise for cancer outcomes, a concept that remains of strong interest today.

In 1956, Rigan [14] completed work on his dissertation, which, again, explored the potential for exercise to protect from cancer and prolong life in the face of cancer. Thirty-seven mice were placed in cages with wheels with counters that quantified the animals' activity level. Thirty-eight mice were placed in cages with restricted activity. All mice were exposed to a carcinogen. Food was controlled to keep weight the same in each mouse upon reaching adulthood. The exercising mice developed cancer later, lived longer overall, and lived longer after the cancer developed.

In 1962, Hoffman [15] published further evidence that exercise slows tumor growth in animals. In an innovative experiment, Hoffman injected saline solution that had bathed the muscles of the exercised mice into mice with larger tumors, and this intervention slowed tumor growth. He concluded that something secreted by the muscles resulted in the tumor growth delay.

Additional early work in 1965 and 1985 again documented that exercise slowed tumor growth in rats and protected the animals from muscle mass loss as cancer progressed [16, 17].

Chapter 4 of this volume presents the most up-to-date review of the preclinical research documenting the mechanisms by which exercise may prevent cancer. Research on mechanistic relationships between exercise and cancer has gained momentum in the last decades, and there is now evidence to support several different potential mechanisms. Chapter 4 reviews tumor cell intrinsic and extrinsic changes induced by exercise, as well as tumor microenvironment changes including changes in the vasculature and immune response to cancer. Epigenetic changes within tumor cells are also reviewed. The authors also highlight emerging mechanisms that are likely to be important for the impact of physical activity on cancer development, treatment, and outcomes.

Clinical Trials in People with Cancer

The earliest publication identified that indicates exercise was used therapeutically with cancer patients is from 1952. Elkins suggests that exercise is useful for improving lymph flow among patients who had undergone mastectomy [18]. The specifics of the exercise are quite different than current recommendations: Isometric exercise was recommended, to avoid the increased blood flow known to accompany isotonic muscle contraction. This differs from today's recommendations that women with and at risk for lymphedema after breast cancer surgery engage in slowly progressive resistance exercise. However, it is notable that exercise was recommended at all in 1952, as there were decades in which any exercise was contraindicated for women who had had breast cancer surgery [19].

An early publication from 1953 also suggests that exercise was used therapeutically for patients with cancer at what is now known as Memorial Sloan Kettering Cancer Center [20]. The author is not provided, but line drawings of women in A-line skirts describe postmastectomy recovery exercises (e.g., wall crawl) and swimming "to train the deltoid and other muscles to carry the function of the lost pectoral muscles." The pamphlet notes that this program of postmastectomy exercise is recommended by the Society of Memorial Center in New York, New York (organization that has become Memorial Sloan Kettering Cancer Center). This suggests a deep history to the exercise and cancer service currently led by Dr. Lee Jones at Memorial Sloan Kettering Cancer Center.

Yet another early reference to the value of exercise within cancer patients was published in 1965. EF Osserman noted that among myeloma patients, there was

complete nonresponse to melphalan, with the exception of two very physically active patients [21]. One was a golfer, the other a swimmer. Notably, the swimmer took issue with the volume of exercise noted in the publication of 100–150 yards/day and published a correction in the journal noting a higher actual daily training volume of 500–550 yards/day [22]. Also notably, Osserman commented that "these ancillary aspects of management must be individualized to the capacities of the individual patients, and, unfortunately, this tailoring is virtually impossible in a cooperative group study with a rigid protocol." Thus, the concept of personalized exercise after cancer appears to extend back to the 1960s. Further, the challenges of exercise trials in the National Cancer Institute cooperative groups have been long understood.

In 1969, the journal *Physical Therapy* published a program for rehabilitation after radical surgery for malignant tumors based on a case series of 21 patients [23]. The objectives of the therapy were to (1) obtain and maintain adequate range of motion in the affected extremity, (2) strengthen remaining muscles in the extremity, (3) prevent deconditioning of uninvolved parts, (4) teach gait and functional activities with assistive apparatus as needed, and (5) to give the patient support and encouragement. Two case studies are provided, one for a male patient with kidney cancer and the other for a male with chondrosarcoma of the scapula. The program of therapy for the kidney cancer patient cannot be described as exercise and mostly included tilt table and passive therapeutic activities. By contrast, the chondrosarcoma patient was prescribed "graded resistive exercises" and passive range of motion activities for the upper body.

The earliest recorded randomized controlled exercise trial that included cancer patients occurred at Ohio State University in 1988, under the direction of nursing scientists, Drs. Winningham and MacVicar [24–26]. In the 1980s while the vast majority of the oncology community was telling patients to "rest, take it easy, don't push yourself," Winningham and MacVicar were testing the effects of supervised exercise on symptom and physiologic responses among women receiving treatment for breast cancer. Their results documented the safety, feasibility, and efficacy for exercise to improve symptoms, aerobic capacity, and body composition. This work was revolutionary for its time.

The number of exercise trials in cancer patients and survivors was low through the 1990s. A review of the literature in 1996 by the authors of two chapters in this volume (Friedenreich (Chap. 3) and Courneya (Chap. 10)) identified 11 studies [27]. Of these, two were unpublished conference proceedings, two were unpublished dissertations, and seven were published in the peer-reviewed literature. Only four were randomized controlled trials. The review concluded that exercise appeared to improve the well-being in breast cancer patients but that the literature had many methodological shortcomings.

A systematic review of exercise and cancer trials in 2005 included 32 studies and 25 outcomes [28]. Weighted mean effect sizes were large for fitness, symptoms during treatment, and vigor after treatment. The majority of the trials at that time had been conducted in patients with breast cancer. Few comments could be made regarding adverse events given studies had not collected or reported data. An update of

that systematic review was published in 2010 that included 82 studies and 66 outcomes [29]. New conclusions in this updated meta-analysis included that exercise could improve strength, fatigue, quality of life, anxiety, and self-esteem in patients during and after cancer treatment. Few adverse events were reported from the 82 trials reviewed. The same year, the first American College of Sports Medicine (ACSM) roundtable guidelines for exercise after a cancer diagnosis were published [30]. Based on the scant evidence at the time, the document focused largely on safety, and the recommendations for exercise were, in large part, based on the 2008 US DHHS Physical Activity Guidelines for all Americans, which started with two words: Avoid Inactivity [31]. Beyond this, the advice was to accumulate 150 min/week of moderate intensity activity, perform twice weekly strength training activities, and do flexibility activities on days when other activities were performed.

In the decade since the publication of the first ACSM, there has been an exponential growth in the field that we now call "exercise oncology." The earliest recorded use of the term exercise oncology seems to be 2005, in a paper by Kerry Courneya and colleagues [32], which included the following sentence: "One important task for *exercise oncology* researchers is to identify the barriers to exercise experienced by cancer survivors to maximize adherence and therefore the benefits of exercise in this population." This statement is still true today.

Over this past decade, the field has grown to the point that we see distinctions that were not previously elucidated regarding the role of exercise across the cancer experience. However, in 2001, Courneya and Friedenreich described a trajectory of outcomes of interest across the cancer control continuum in the PEACE Framework, that all but predicted what the literature now supports [33]. PEACE stands for Physical Exercise Across the Cancer Experience. Prior to the existence of any clinical trials to guide this thinking, the authors understood that what the patient and clinician would be focused on would vary from the point of diagnosis through treatment and beyond. Today there are trials specific to pretreatment in a nascent field of "prehabilitation," which explores the potential for interventions (including exercise) performed prior to anticancer therapy to improve outcomes during and after cancer treatment. This growing field is reviewed in Chap. 6. This is followed by a review of what we know of the value of exercise in the setting of surgical recovery in Chap. 7. Chapters 8 and 9 review the clinical trial evidence supporting the use of exercise as a beneficial therapy during infusion and radiation therapy, respectively. Dr. Courneya provides a review of the growing evidence regarding exercise for treatment tolerance and efficacy in Chap. 10. Part 2 of this volume would have been a scant chapter a decade ago. Several chapters are based on such recent science that they would not have been mentioned at all in 2010.

In Part 3 of this volume, we focus on the time frame from the end of treatment to the end of life. In this section are chapters reviewing the efficacy of exercise to improve outcomes immediately following treatment (Chap. 12), when the focus is on recovery of function, as well as long-term outcomes (Chap. 13). In addition, the growing field of cardio-oncology is reviewed in Chap. 14. Cardio-oncology is a growing field that aims to optimize cardiovascular outcomes among those diagnosed with cancer. Chapter 14 includes observational evidence, inferences from related fields, and the correlational science that has been completed to date. The

focus on energy balance or "energetics" is not new, as noted by the historical commentary at the start of this chapter. But the latest evidence of the relationship between exercise, diet, and body weight for cancer prevention, survival, and related outcomes is reviewed in Chap. 15. Finally, the literature on the role of exercise for patients with advanced cancer, undergoing palliative treatments, or at the end of life is reviewed in Chap. 16.

Behavioral, Logistical, and Policy Issues in Exercise Oncology

In Part 4 of this volume, we review all of the additional issues that require attention for exercise oncology to become the standard practice for people living with and beyond cancer: behavioral and logistical issues, as well as the challenges of working in a multidisciplinary field, and, finally, policy challenges that are key to making exercise the standard practice for people living with and beyond cancer.

Chapter 17 starts with the simple observation that despite the issuance of guidelines in several countries to encourage cancer survivors to adopt physical activity (PA), the proportion of survivors' exercising at recommended levels is low. As such, there is a need to discern the behavioral barriers to cancer patients and survivors becoming and staying physically active. Reviews of theory-based physical activity behavior change programs are provided, as well as a status update on efforts to sustain PA. The authors discuss the need for behavior change not only of the individual survivor but also of their families, peers, friends, and healthcare providers. The potential use of technologies to overcome barriers to physical activity is also discussed. This chapter closes by pointing to future directions to make achievement of PA guidelines a reality for the growing number of cancer survivors worldwide.

Chapter 18 focuses on the logistical challenges to getting and staying more active among people living with and beyond cancer. Recommendations include development of diverse programming options, as well as addressing the ongoing, thorny issue of triage and referral.

The question of how best to connect those living with and after cancer with appropriate exercise or rehabilitative programming is long standing. Two early studies in this area, from 1982 and 1984, respectively [34, 35], tested whether exercise testing would improve the prediction of morbidity, mortality, and functional outcomes after lung resection. Both studies concluded that pulmonary function tests were better predictors of outcomes in patients scheduled for a lung resection than exercise testing. In contrast, in 1984 another study documented that maximal aerobic fitness (VO2 max) was predictive of cardiopulmonary complications among thoracotomy patients [36]. Only one in ten patients with a VO2 max of 20 ml/kg/min or greater had complications post-surgery, compared to all six patients with a VO2 max of 15 ml/kg/min or less. This shows that there has been interest in predicting outcomes in cancer patients for decades and that the question of whether to perform specific testing has been asked just as long. Chapter 18 concludes by setting research priorities focused on dissemination and implementation to help move research findings into practice.

In Chap. 19, this volume addresses the "elephant in the room" of exercise oncology: multidisciplinarity. There are many types of professionals, with disparate training, who can approach the triage, referral, and intervention aspects of exercise oncology practice with patients living with and beyond cancer. Questions of how these professionals should collaborate toward the goal of maximizing patient outcomes remain largely unanswered, but concepts and ideas are put forward in Chap. 19. The author notes that that the factors that determine which type of provider should consult on a patient will change over time, and as such, the need for multidisciplinary involvement needs to be regularly reevaluated. In Chap. 19, a framework to aid decisions on this topic is discussed and illustrated using cases.

Chapter 20 addresses the challenges of policy, which underlie access to exercise programming for both current patients and survivors. The policy levers that influence exercise access are discussed, including reimbursement and whether healthcare providers are incentivized to provide programming. Other policies that influence the range and quality of exercise programming that may be available to a cancer survivor are also discussed, including triage and referral, provider training, on-site facilities and services, and provision of patient education. This chapter provides an overview of the diverse reimbursement (and non-reimbursement) policies in the commercial, governmental, and organizational sectors that influence exercise programming for cancer survivors. The chapter concludes with the need for multipronged policy initiatives that in concert raise awareness, educate providers, enhance quality, and ensure access.

Conclusion

In summary, the history of writings on exercise for health *and* cancer reaches deep into antiquity. First mention of the role of exercise in prevention of cancer reaches back over 100 years, and preclinical evidence that exercise may slow tumor growth first emerged more than 80 years ago. That said, the concept of exercise for prevention and as a therapeutic intervention during and after treatment remained relatively esoteric for many years. The field of exercise oncology, named in 2005, really gained momentum in the past decade. Several chapters in this volume could not have been written due to lack of evidence a decade ago. Within these pages are contained the latest science regarding the role of exercise for cancer prevention, mechanisms through which that prevention might occur, and exercise as a therapeutic intervention after cancer diagnosis and for the balance of life. Read for yourself and decide if we have come to a tipping point where exercise should become standard practice for cancer prevention and therapy after diagnosis. If we have, Part 4 may become our roadmap to the future, by addressing the behavioral, logistic, multidisciplinary, and policy issues to making assessment, advice, and referral to exercise standard practice for people living with and beyond cancer.

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Part I
Physical Activity and Cancer Prevention

Chapter 2
Primary Prevention

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Physical Activity, Sedentary Behavior, and the Primary Prevention of Cancer

One in three people in the United States will be diagnosed with cancer in their lifetime [1].

This burden can be greatly reduced through primary prevention, defined as the intervention of health behaviors or exposures before a disease develops. The benefits of engaging in behaviors associated with lower cancer risk, such as avoiding tobacco smoke and alcohol, maintaining a healthy body weight, consuming a healthy diet, and engaging in physical activity, are well documented [2, 3]. In fact, the primary prevention of cancer through physical activity alone can have a large public health impact, as some estimates suggest that physical inactivity accounts for approximately 2.9% of all cancer cases in the United States [4].

Physical activity is a multifaceted, complex behavior. The dosage of physical activity can be determined through the FITT principle, wherein the *F*requency (i.e., days per week), *I*ntensity, *T*ime (i.e., duration, generally hours per week), and *T*ype of activity together quantify the total dose. Physical activity intensity, categorized as light, moderate, or vigorous, refers to the average metabolic cost of an activity. Light-intensity activities require little effort, with a metabolic equivalent level (MET, the ratio of the active metabolic rate to the resting metabolic rate) between 1.6 and 2.9 [5]. Examples of light-intensity activities include walking at a leisurely pace, folding laundry, and taking a shower. Moderate-intensity activities, such as brisk walking or dancing, require a bit more physical effort at 3–5.9 METs. Vigorous activities, which require much more effort (6+ METs) and cause a significant increase in respiratory and heart rate, include jogging/running, soccer, cross-country skiing, and boxing. Type

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of physical activity refers to the mode of exercise, including aerobic (e.g., biking, walking, hiking, or running) or muscle-strengthening activities (e.g., weight lifting or calisthenics). Approximate MET values of various types of physical activities are documented in the Compendium of Physical Activities [5]. The total physical activity quantity or dose is calculated by multiplying the MET value of each activity by the time spent in that activity and summing all activities done during a specified period (most often 1 week) to obtain the overall number of MET-hours of physical activity.

All waking behavior is classified as either physical activity (of light, moderate, or vigorous intensity) or sedentary behavior. Sedentary behavior includes any waking behavior performed while sitting, reclining, or lying that is characterized by a low-energy expenditure ($\leq$1.5 METs) [6]. Although sedentary time does not solely consist of sitting, these behaviors are usually quantified by sitting duration (i.e., total sitting time) or duration in a specific domain or context (i.e., total television viewing time or total occupational sitting time) in epidemiologic studies [6, 7]. Evidence suggests that physical activity and sedentary behavior, though related, may be independently associated with adverse health outcomes [8–10].

There are specific recommendations for a minimum physical activity dose for cancer prevention. The American Cancer Society (ACS) suggests that adults limit sedentary behavior and engage in at least 150 minutes of moderate-intensity (the equivalent of $\geq$7.5 MET-hours/week) or 75 minutes of vigorous-intensity physical activity each week (or an equivalent combination), and for greater cancer prevention benefits, these guidelines should be doubled [11]. The 2018 Physical Activity Guidelines for Americans, although not specifically geared toward cancer prevention, is largely consistent with the ACS guidelines and recommends aerobic activity for at least 150–300 minutes per week of moderate intensity, or 75–150 minutes per week of vigorous-intensity aerobic physical activity, or an equivalent combination. The Physical Activity Guidelines for Americans also recommends that muscle-strengthening activities of moderate or greater intensity involving all major muscle groups should be done 2 or more days per week [12]. A level of physical activity less than these guidelines is referred to as physical inactivity or an "insufficient" amount of physical activity [6].

Although the existing evidence supports the case that population increases in physical activity and decreases in sedentary time would lead to reductions in cancer risk, there is still much work to be done to fully understand these relationships. This chapter will cover the current epidemiologic evidence for the potential associations between physical activity, sedentary time, and the risk of total and site-specific cancer incidence. Current gaps in the literature and potential limitations in the study of physical activity and cancer will also be covered.

Physical Activity, Sedentary Time, and Total Cancer Risk

There is a growing body of epidemiologic evidence suggesting that physical activity is protective against the risk of cancer occurrence. While it is certain that the association between physical activity and risk of cancer differs by cancer site, assessing total cancer outcomes may be informative in some instances and can alleviate issues

with statistical power (e.g., small number of site-specific cancer cases). Cancer mortality endpoints are a crude way of examining primary prevention given the representation of both cancer incidence and subsequent survival. However, the evidence base of physical activity and total cancer mortality is extensive and may therefore provide useful insights for understanding the broader public health impact of physical activity.

A recent meta-analysis including 42,428 cancer deaths observed that engaging in high levels, compared to low levels, of physical activity was associated with a 21% decreased risk of cancer mortality (95% confidence interval [CI], 0.75–0.85) [13]. Another study which pooled data from six cohorts found that accumulating an amount of leisure-time physical activity equivalent to approximately two to three times the physical activity guidelines was associated with a 25% reduced risk of cancer mortality compared to engaging in no leisure-time activity (95% CI, 0.72–0.79) [14]. Another meta-analysis of 71 prospective cohort studies considered the relationship between physical activity and risk of cancer mortality in more detail and observed a dose-response relationship that showed accumulating a minimum of 2.5 hours/week of moderate-intensity physical activity is associated with a 13% reduction in cancer mortality [15].

In studies of total cancer incidence, estimates for the association with physical activity are often aggregated estimates of associations with risk of site-specific cancer. For example, a large pooled analysis of 12 prospective cohorts (including 1.44 million participants and 186,932 cancer cases) by Moore et al. compared risk of 26 cancer types in the 90th to the 10th percentile of leisure-time physical activity and reported that higher levels of physical activity were associated with a 7% lower risk of total cancer according to the aggregate estimate (hazard ratio [HR], 0.93; 95% CI, 0.90–0.95) [16]. Similarly, one meta-analysis pooled studies of site-specific cancer incidence to examine the association of leisure-time physical activity and multisite cancer incidence [17]. This study found that, compared to reporting no leisure-time physical activity, reporting modest amounts of leisure-time physical activity was associated with a lower risk of total cancer incidence (10 MET-hours/week, relative risk [RR], 0.93; 95% CI, 0.91–0.95). It is important to note that this study did not include all cancer sites and only pooled studies of breast, colorectal, prostate, lung, pancreatic, endometrial, ovarian, and lymphoid cancers.

Evidence for an association between sedentary behavior and risk of cancer has emerged over the last decade and is somewhat limited. The first comprehensive meta-analysis of associations between sedentary behavior and cancer mortality observed a 12% increased risk of dying from cancer with the highest (vs. lowest) levels of sedentary behavior overall [18]. On the other hand, a large harmonized meta-analysis including over 30,000 cancer deaths reported that there was no evidence of an overall dose-response relationship between total sitting time and cancer mortality [9]. However, in the lowest quartile of physical activity, there was a 21% increased risk of cancer mortality in those who reported sitting more than 8 hours/day (HR, 1.21; 95% CI, 1.14–1.28). Similarly, in the second physical activity quartile, there was an 8% increased risk of cancer mortality in those who reported sitting for more than 8 hours/day (HR, 1.08; 95% CI, 1.00 to 1.15). Based on this study, it is possible that excess sitting time may be positively associated with cancer mortality among those who are physically inactive.

When examining cancer incidence, one meta-analysis including seven studies of non-Hodgkin's lymphoma and breast, ovarian, colon, and endometrial cancers found that high sedentary time was associated with a higher risk of these aggregate cancers (HR, 1.13; 95% CI, 1.05–1.21) [19]. A large prospective cohort study that was not included in this meta-analysis, however, did not see a statistically significant association between sitting and risk of total cancer among men (sitting for at least 6 hours/day sitting compared to less than 3 hours/day, RR, 1.00; 95% CI, 0.96–1.05) but found that excess sitting was associated with a 10% higher risk of total cancer among women only (RR, 1.10; 95% CI, 1.04–1.17) [20].

Physical Activity, Sedentary Time, and Site-Specific Cancer Risk

There are over 100 types of cancer, including various cancer subtypes. Given all we know about the etiologic and pathologic heterogeneity of each cancer site, it is likely that physical activity is more important for the prevention of certain cancer sites over others. Physical activity and cancer research has expanded in the past decade, and as a result, several expert groups have summarized recent findings for the associations between physical activity and the risk of site-specific cancer. According to the World Cancer Research Fund's (WCRF) Third Expert Report, there is convincing evidence of an association between physical activity and decreased risk of colon cancer, and there is evidence for a probable association between physical activity and decreased risk of postmenopausal breast and endometrial cancers [21]. Evidence is less conclusive and therefore graded as limited but suggestive for the association between physical activity and decreased risk of cancer of the esophagus, lung, liver, and breast (premenopausal). Given the different grading criteria, the 2018 Physical Activity Guidelines Advisory Committee (PAGAC) Report graded the protective association with physical activity as strong with risk of the following cancers: bladder, breast, colon, endometrial, esophageal, gastric, and renal [12]. The PAGAC also graded the evidence as moderate for lung cancer and limited for head and neck, hematologic, ovary, pancreas, and prostate cancers. The most recent expert review on physical activity and cancer risk, a roundtable report led by the American College of Sports Medicine (ACSM), did not assign specific grades, but conclusions were consistent with PAGAC for the seven cancers with strong evidence for an association with physical activity [22]. The ACSM roundtable report differed from the PAGAC report in a few areas, but this was largely because newer evidence was available at the time of the ACSM report. For example, the ACSM expert panel reported that physical activity may also protect against the risk of liver cancer. Additionally, while PAGAC graded the evidence for lung cancer as moderate, the ACSM expert panel felt the evidence for an association between physical activity and a reduced risk of lung cancer was limited given the susceptibility of the association to confounding by smoking.

There is some evidence to support the positive association between sitting time and some types of cancer, but the exact amount or domain of sitting time that may be associated with increased cancer risk remains unclear. The WCRF has listed an association between sedentary behavior and only endometrial cancer as limited-suggestive [21]. The 2018 PAGAC Report concludes that there is moderate evidence for a significant relationship between greater time spent in sedentary behavior and higher risk of endometrial, colon, and lung cancer [12].

Cancer sites graded as having strong or moderate evidence for an association with physical activity by the 2018 PAGAC are highlighted in more detail below, and a summary of PAGAC and WCRF Report findings can be found in Tables 2.1 and 2.2. Many of the studies discussed below quantify cancer risk for high versus low levels of physical activity. For more commonly studied cancers, including colon and breast, some studies have more carefully examined the dose-response relationships; where available, this information will be discussed.

Table 2.1 Physical activity and decreased risk of cancer

Cancer site	WCRF/AICR 2018 grade[a]	PAGAC 2018 grade[b]
Breast (premenopausal)	Probable[c]	Strong
Breast (postmenopausal)	Probable	Strong
Bladder	–	Strong
Colon	Convincing	Strong
Endometrium	Probable	Strong
Esophagus	Limited-suggestive	Strong[d]
Gastric	–	Strong
Head and neck	–	Limited
Hematologic	–	Limited
Liver	Limited-suggestive	–
Lung	Limited-suggestive	Moderate
Ovary	–	Limited
Pancreas	–	Limited
Prostate	–	Limited
Renal	–	Strong

[a]Full WCRF/AICR grading criteria available in Appendix 1 of 2018 Report [21]
[b]Evidence grade refers to strength of evidence in the literature regarding associations between physical activity and cancer risk [12]
[c]For vigorous-intensity physical activity
[d]Grade for esophageal adenocarcinoma

Table 2.2 Sedentary behavior and increased risk of cancer

Cancer site	WCRF/AICR 2018 grading[a]	PAGAC 2018 grading[b]
Colon	–	Moderate
Endometrium	Limited-suggestive	Moderate
Lung	–	Moderate

[a]Full WCRF/AICR CUP grading criteria available in Appendix 1 of 2018 Report [21]
[b]Evidence grade refers to strength of evidence in the literature regarding associations between physical activity and cancer risk [12]

Colon Cancer

Reflecting the large body of high-quality epidemiologic evidence on what is perhaps the most commonly studied cancer in physical activity epidemiology, PAGAC and WCRF grade the evidence for the association of physical activity with the risk of colon cancer as strong [12, 21]. Physical inactivity accounts for a large number of colon cancer cases, with an estimated 16.3% of all colorectal cancer cases attributable to physical inactivity [4].

Two meta-analyses suggest that high levels of physical activity are associated with an approximate 19% decreased risk of colon cancer [13, 17]. The large pooled analysis by Moore et al. similarly found that high levels of physical activity were associated with a 16% lower risk of colon cancer (95% CI 0.77–0.91) [16]. Importantly, sufficient evidence suggests that excess body fatness may increase the risk of colon cancer [23], meaning body fatness may be a potential mediating factor between physical activity and the lower risk of colon cancer.

There have been a few studies exploring associations with colon cancer subsites, including proximal and distal colon cancer, and for the most part, it appears the associations with physical activity are very similar. One meta-analysis of 21 studies found that the risk of proximal colon cancer was 27% lower among the most active compared to the least active (95% CI 0.66–0.81) and the risk of distal colon cancer was 26% lower among the most active (95% CI 0.68–0.80) [24]. These results were confirmed by another meta-analysis of 30 studies that reported similar findings (proximal, RR, 0.76; 95% CI, 0.70–0.83, distal, RR, 0.77; 95% CI, 0.71–0.83) [25]. Colon cancer is often grouped together with rectal cancer (i.e., colorectal cancer). However, there appears to be some heterogeneity in the associations of physical activity and risk of colon and rectal cancers. The evidence for the association between physical activity and risk of rectal cancer is limited and inconsistent. Some studies have reported no association between physical activity and risk of rectal cancer, [25] and some report a reduction in risk (HR, 0.87; 95% CI, 0.80–0.95) [16].

The PAGAC states that the evidence for a dose-response relationship between increasing physical activity and decreasing risk of colon cancer is strong [12]. This grade is based on a few studies, including the large pooled analysis, which found a significant inverse relationship between leisure-time physical activity and risk of colon cancer ($P_{overall} < 0.0001$) [16]. Additionally, the WCRF dose-response meta-analysis found that per 30 daily minutes of recreational physical activity, the relative risk of colon cancer was 0.88 (95% CI, 0.80–0.96) [21].

The PAGAC grades the evidence for an association between sedentary time and risk of colon cancer as moderate. One meta-analysis of 43 studies compared the highest and lowest levels of total sitting time, and the relative risk for colon cancer was 1.24 (95% CI, 1.03 to 1.50) [26]. A newer meta-analysis reported a stronger association with occupational sedentary time, where high levels of occupational sedentary time were associated with a 44% higher risk of colon cancer (95% CI, 1.28, 1.62) [27].

Breast Cancer

Like colon cancer, there is large body of high-quality epidemiologic evidence suggesting that physical activity could significantly reduce the risk of breast cancer. Accordingly, the evidence for an inverse association between physical activity and the risk of breast cancer was found to be strong by PAGAC [12]. An estimated 3.9% of female breast cancer cases are attributable to physical inactivity [4].

The large pooled analysis comparing high and low levels of physical activity reported a 10% lower risk of breast cancer among the highly active (HR, 0.90; 95% CI, 0.87–0.93) [16]. These results are similar to two meta-analyses which reported that high versus low levels of physical activity were associated with a 12–13% lower risk of breast cancer (RR, 0.87; 95% CI, 0.84–0.90; RR, 0.88; 95% CI, 0.85–0.91) [13, 28]. Similar to colon cancer, it is possible that excess body fatness is a mediating factor between physical activity and lower risk of breast cancer [23]. Studies suggest that physical activity may be associated with greater breast cancer risk reductions in women with a body mass index (BMI) < 25 kg/m^2 compared to women with a BMI ≥ 25 kg/m^2 [29, 30].

The PAGAC also grades the evidence for a dose-response relationship between increasing physical activity and decreasing risk of breast cancer as strong [12]. Moore et al. reported a linear dose-response relationship between increasing levels of leisure-time physical activity and decreased breast cancer risk ($P < 0.0001$) [16]. Another dose-response meta-analysis suggested that the risk of breast cancer decreased by 5% for every 2 hours/week increment in moderate-to-vigorous recreational activity ($P < 0.001$) [28].

The WCRF grades the evidence for breast cancer risk by menopausal status and finds the evidence to be limited but suggestive for an association between physical activity and risk of premenopausal breast cancer and probable for risk of postmenopausal breast cancer [21]. One meta-analysis included 43 studies of premenopausal and 58 studies of postmenopausal breast cancer and found that high levels of physical activity were associated with very similar relative risks for the two subtypes (RR, 0.80; 95% CI, 0.74–0.87 premenopausal and RR, 0.79; 95% CI, 0.74–0.84 postmenopausal) [30]. Another meta-analysis, on the other hand, reported stronger associations among premenopausal women (RR, 0.77, 95% CI, 0.72–0.84) than postmenopausal women (RR, 0.88, 95% CI, 0.87–0.92) [28]. There are fewer studies exploring the possibility of etiologic heterogeneity of the associations with physical activity by estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor type 2 receptor (HER2) status.

Evidence for a dose-response relationship by menopausal status is more limited, but one study found a statistically significant, curvilinear dose-response relationship with physical activity for the risk of both pre- and postmenopausal breast cancers [30]. The authors of this study speculated that the nonlinear relationship may reflect a point of diminishing returns beyond 20–30 MET-hours/

week of moderate-to-vigorous physical activity or the small number of participants accumulating very high levels of physical activity (i.e., large confidence intervals).

Endometrial Cancer

The evidence base for the association between physical activity and cancer of the endometrium (corpus uteri) is considered strong and probable by the PAGAC and WCRF, respectively. In a recent study of the proportion of cancer cases attributable to modifiable risk factors, physical inactivity accounted for 26.7% of cancers of the corpus uteri [4].

According to the two meta-analyses and the pooled analysis that explored the association between physical activity and risk of endometrial cancer, it is estimated that high levels of physical activity are associated with an approximate 17–21% lower risk of endometrial cancer [13, 16, 31]. It is likely, however, that excess body fatness is also a potential mediating factor between physical activity and lower risk of endometrial cancer [32]. This is demonstrated in the large pooled analysis, where the overall hazard ratio for the relationship is 0.79 (95% CI 0.68–0.92), but the relationship is null in those with a BMI lower than 25 kg/m^2 (P for heterogeneity <.001) [16].

The PAGAC and WCRF have graded the evidence for the association between sitting and an increased risk of endometrial cancer as moderate and limited-suggestive, respectively. There are far fewer studies of the relationship between sedentary time and risk of endometrial cancer, but a recent meta-analysis of eight studies reported a significant association between sitting while watching television and risk of endometrial cancer (RR, 1.36; 95% CI, 1.15–1.60) [26].

Bladder Cancer

According to the PAGAC, strong evidence suggests that greater amounts of physical activity are associated with reduced risk of developing bladder cancer [12], but the WCRF finds the evidence to be too limited to draw conclusions [21]. One of the few meta-analyses dedicated to bladder cancer incidence included 18 risk estimates (from both cohort and case-control studies) and found a significant inverse association between physical activity and risk of bladder cancer (RR, 0.85; 95% CI, 0.74–0.98 for high vs. low physical activity) [33]. Similarly, the pooled analysis, which included 9073 bladder cancer cases, reported a 13% lower risk of bladder cancer for the 90th versus 10th percentile of leisure-time physical activity (HR, 0.87; 95% CI, 0.82–0.92) [16]. However, since the PAGAC and WCRF Reports were released, a meta-analysis of 11 studies reporting no association between high levels of physical activity and risk of bladder cancer was published [13].

Esophageal Cancer

The WCRF grades evidence as limited but suggestive for an inverse association between physical activity and risk of esophageal cancer [21]. According to the PAGAC report, which separately assessed the two major esophageal cancer subtypes, there is strong evidence for an inverse association between physical activity and risk of esophageal adenocarcinoma and limited evidence for an association with risk of esophageal squamous cell carcinoma [12].

The strongest association with physical activity among the 26 cancer types assessed in the pooled analysis was for the risk of esophageal adenocarcinoma (HR, 0.58; 95% CI, 0.37–0.89) [16]. Effect modification by BMI was not statistically significant for the association of physical activity with esophageal adenocarcinoma in the pooled analysis ($p = 0.60$), but when results were stratified, the relationship was statistically significant only among those with a BMI of at least 25 kg/m^2. Other studies suggest that esophageal adenocarcinoma may be associated with obesity, making BMI a potential mediating factor between physical activity and lower risk of this cancer [34]. Esophageal squamous cell carcinoma makes up 87% of all esophageal cancers, making it much more common than esophageal adenocarcinoma [35]. However, evidence for a significant inverse association with physical activity is limited, as both the pooled analysis (HR, 0.80; 95% CI, 0.61–1.06) [16] and a meta-analysis (RR, 0.94; 95% CI, 0.41–2.16) [36] reported nonsignificant associations.

Gastric Cancer

The PAGAC report states that there is strong evidence for the association of greater amounts of physical activity and reduced risk of developing gastric cancer. One of the larger meta-analyses on the topic, which included ten cohort studies (including 7551 incident cases) and 12 case-control studies (5803 cases), found that any level of physical activity, compared to none, was associated with a lower risk of all gastric cancer (RR, 0.81; 95% CI, 0.73–0.89) [37]. Similarly, the pooled analysis reported a significant inverse association with high vs. low levels of physical activity and risk of gastric cancer (HR, 0.78; 95% CI, 0.64–0.95) [16]. Importantly, the pooled analysis showed significant effect modification by BMI ($p = 0.02$), where the association with physical activity was not significant among those with a BMI less than 25 kg/m^2 [16]. This is plausible as gastric cardia is known to be associated with obesity [34].

Like esophageal cancer, it is important to the etiology of gastric cancer to consider common subtypes. Gastric cancer subtypes are classified according to the anatomic site as follows: (a) cardia, the upper part of the stomach, and (b) non-cardia, the mid and distal stomach. While there may be etiologic heterogeneity between the two major subtypes, the few studies that explored subtype differences do not seem

to suggest that physical activity is differentially associated with risk of cardia and non-cardia gastric cancer. A large meta-analysis, for example, found similar relative risk estimates for the association between physical activity and gastric cardia adenocarcinoma (RR, 0.83; 95% CI, 0.69–0.99) and gastric non-cardia adenocarcinoma (RR, 0.72; 95% CI, 0.62–0.84) [36].

Lung Cancer

Studies of the association between physical activity and risk of lung cancer have mixed results, and for that and other reasons, the PAGAC and WCRF have graded evidence for an association as moderate and limited-suggestive, respectively. While a few studies and meta-analyses have reported a significant inverse association [13, 38, 39] or no association between physical activity and risk of lung cancer [17], almost all studies that assess these associations by smoking status seem to suggest that residual confounding by smoking may be a possible explanation for the relationships observed. Because of these inconsistencies and the likelihood for confounding, the ACSM expert panel also stated that the evidence for a true association is unclear.

Several studies have shown that physical activity is unrelated to the risk of lung cancer among never smokers but may be inversely associated with the risk of lung cancer among former and current smokers [16, 38, 40, 41]. For example, one meta-analysis of cohort studies looking at the association among the three smoking groups found that the physical activity was associated with a 32% lower risk of lung cancer among former smokers and a 20% lower risk of lung cancer among current smokers (RR, 0.68; 95% CI, 0.51–0.90 and RR, 0.80; 95% CI, 0.70–0.90) [41]. This association was null among those who have never smoked (RR, 1.05; 95% CI, 0.78–1.40). Effect modification by smoking status was also statistically significant in the pooled analysis ($p < .001$) [16].

There has been one meta-analysis suggesting an association between excess sitting while watching television and risk of lung cancer [26]. However, since that meta-analysis was published, there have been several cohort studies that did not observe significant associations between sedentary behavior and risk of lung cancer [20, 39]. It is likely that residual confounding by smoking may help explain the differences observed.

Renal Cancer

The PAGAC Report graded evidence demonstrating that greater amounts of physical activity are associated with reduced risk of developing renal cancer as strong, but the WCRF deemed the evidence too limited to draw a conclusion. Playing a role

in the PAGAC decision, one meta-analysis of 19 studies reported that high levels of physical activity were associated with a 12% reduced risk of renal cancer (RR, 0.88; 95% CI, 0.79–0.97), though this association was strengthened when estimates from only high-quality studies were considered (RR, 0.78; 95% CI, 0.66–0.92) [42]. The pooled analysis reported a stronger risk estimate, where high levels of physical activity were associated with a 23% lower risk of renal cancer (RR, 0.77; 95% CI, 0.70–0.85). Effect modification by BMI in the pooled analysis was not statistically significant for renal cancer ($p = 0.56$) [16], although renal cancer is thought to be obesity-related [34].

Limitations and Gaps in the Study of Physical Activity for the Primary Prevention of Cancer

Studying Associations of Physical Activity with Risk of Rare Cancers

The National Cancer Institute defines rare cancers as those with fewer than 15 cases per 100,000 people per year. Overall, 5-year survival rates for rare cancers are low; therefore, the identification and promotion of lifestyle behaviors amenable to prevention could have a marked impact on morbidity and mortality [43]. Given the inherent small number of cases available in cohort studies, pooled analyses are needed to study potential associations of physical activity or sedentary behavior with rare cancers. While very limited evidence exists for rare cancers, associations with physical activity have not been ruled out. For example, small intestine and gallbladder cancers are considered rare, and both were included in the large pooled analysis with borderline significant inverse associations (HR, 0.78; 95% CI, 0.60–1.00 for risk of small intestine cancer and HR, 0.72; 95% CI, 0.51–1.01 for risk of gallbladder cancer) [16]. While it is possible that physical activity and sedentary behavior are associated with the risk of additional cancer types, more research is needed to understand these relationships.

Measurement of Physical Activity and Sedentary Behavior

Most of the observational studies cited in this chapter relied on self-reported, self-administered surveys of physical activity and sedentary behavior. Self-reported measures are currently the most feasible option for large-scale studies because of the low cost and ease of administration, but the use of these measures may be limited by participant comprehension, social desirability bias, participants' difficulty recalling physical activity and sedentary time, or other sources of random and

systematic error [44–46]. Further, there are hundreds of existing self-reported measures of physical activity and sedentary time, many of which vary greatly in the time frame queried, domains assessed, and metrics evaluated. This means that comparing results across studies that use different survey questions can be difficult. Additionally, most studies assess habitual physical activity and sedentary time through surveys administered at a single time point, leading to potential non-differential misclassification due to changes in physical activity throughout the life course.

Objective measures of physical activity and sedentary time, such as accelerometers, have several advantages over self-reported measures. Accelerometers are wearable devices that objectively measure the acceleration of bodily movement. These data are used to estimate time in activity intensity categories. Accelerometers perform well for estimating moderate-to-vigorous-intensity physical activity time and are notably more accurate than surveys for measuring light-intensity physical activity time. Additionally, accelerometers with built-in inclinometers can measure postural changes (i.e., sitting vs. standing) and are therefore better for quantifying sedentary time than surveys. However, accelerometers require extensive data processing and are more costly than surveys, and they don't collect information regarding domain or context [47, 48]. Objective and self-reported measures of physical activity and sedentary time are vastly different, yet both have strengths and limitations. Hence, population-based monitoring of these behaviors may benefit from incorporating both self-reported and device-based measures to fully capture the multifaceted aspects of the movement behaviors [49].

Prescribing Exercise for Cancer Prevention

Estimates of association in observational studies, like most of the studies cited throughout this chapter, cannot be interpreted as measures of effect. To quantify the effects of physical activity or sedentary behavior on cancer risk, randomized controlled trials with cancer incidence endpoints must be conducted. However, the necessary length of follow-up and the very large sample size that would be required for these studies mean that observational studies will likely continue to be the main method for studying the relationships between physical activity, sedentary time, and cancer risk. The limitations of observational studies and the self-reported measures used in observational studies have led to a limited understanding of the dose-response association by cancer site. This gap in the literature makes the prescription of exercise for cancer prevention difficult.

Aerobic physical activity is the most frequently studied component of exercise in cancer epidemiology. Many studies compare risks for high and low levels of moderate-to-vigorous-intensity aerobic physical activity (MVPA), although detailed physical activity dose information would be ideal for pinpointing more specific beneficial amounts. Despite the research gaps, MVPA recommendations for the prevention of cancer exist [11].

There is far less evidence for associations of other components of physical activity and risk of cancer. While muscle-strengthening activities are undoubtedly beneficial for muscle mass, bone strength, and functional health [50, 51], the evidence for benefits regarding cancer prevention is very limited [12]. Among the few studies on the topic, data from the Women's Health Study found no association between strength training and risk of cancer mortality [52]. Similarly, a smaller cohort study found that engaging in muscle-strengthening activities was not associated with risk of cancer mortality (HR, 0.92; 96% CI, 0.45–1.86) but did find that the top quartile of lower extremity muscle strength was associated with a 50% lower risk of cancer mortality (HR, 0.50; 0.29–0.85 vs. lowest quartile) [53]. It is clear that muscle-strengthening activities should be prescribed by exercise professionals in general, but more research may be needed to include these activities in guidelines geared specifically toward cancer prevention. Similarly, insufficient epidemiologic evidence exists on associations between light-intensity physical activity, sedentary time, and cancer risk, hindering the development of clear recommendations for cancer prevention. The 2018 Physical Activity Guidelines for Americans includes the general phrase, "move more, sit less"; however, current research is not robust enough to allow for much more specific recommendations regarding excess sedentary time and cancer prevention.

Summary

In the last decade alone, numerous studies have clarified the role of physical activity in the primary prevention of cancer. In addition to the well-established associations of physical activity with the decreased risk of colon, breast, and endometrial cancers, recent studies have further identified potential associations between physical activity and decreased risk of esophageal, liver, bladder, gastric, and renal cancers. While evidence is too limited to draw conclusions, a few studies suggest that there may also be an association between physical activity and pancreas, ovary, head and neck, prostate, and hematologic cancers. Similarly, a few recent studies suggest that there may be an association between excess sitting time and increased risk of colon and endometrial cancer.

Despite all we have learned, more research is needed before we can confidently and completely prescribe exercise specifically for cancer prevention. Similarly, more studies are necessary to develop prescriptions for sedentary behavior beyond the very general "move more, sit less" recommendation. However, evidence suggests that using the American Cancer Society's guidelines for cancer prevention and/or the Physical Activity Guidelines for Americans as a guide for minimum exercise prescriptions may reduce the risk of cancer.

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Chapter 3
Physical Activity and Cancer Survival

Christine M. Friedenreich, Chelsea R. Stone, and Sandra C. Hayes

Introduction

Current physical activity guidelines generated by the World Health Organization (WHO) recommend that the general population participate in at least 150 minutes of moderate aerobic physical activity per week (equivalent to 75 minutes of vigorous aerobic physical activity) in bouts of 10 minutes or more [1]. Guidelines for cancer survivors produced by the World Cancer Research Fund/American Institute for Cancer Research recommend that cancer survivors engage in regular physical activity following guidelines for the general population and further recommend that survivors should return to normal daily activities as soon as possible following diagnosis [2–4]. In 2018, the Clinical Oncology Society of Australia delivered a position statement on exercise in cancer care in which they recommend that exercise should be "embedded as part of standard practice in cancer care and to be viewed as an adjunct therapy that helps counteract the adverse effects of cancer and its treatment" [5]. This position statement raised some concerns in the exercise oncology community since the state of evidence regarding the feasibility, suitability, type, and dose of activity that should be recommended for all cancer patients and survivors remains unclear. Recognition exists, nonetheless,

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regarding the vital role that physical activity has during treatment, rehabilitation, and survival for cancer despite a lack of evidence in some areas. Furthermore, the field of precision medicine has also been applied to physical activity and cancer in a seminal paper led by Jones (2016) in which a framework for precision exercise oncology was provided [6]. In this chapter, we review the evidence on physical activity and survival in cancer populations while also providing insight into some elements of precision exercise oncology in efforts to discern which cancer patient and survivor groups could experience particular survival benefits with regular physical activity. The primary reviews of the evidence will focus on physical activity as it was reported in the included studies.

Physical Activity and Cancer Survival: Epidemiologic Research

The first study investigating the relationship between physical activity and survival outcomes in cancer survivors was published in 1992 [7]. However, this area of research did not garner much traction until 2005. Since then, there has been an exponential increase in the number of studies published evaluating the association between physical activity and mortality outcomes among cancer survivors. By 2019, identified through searches in PubMed, EMBASE, and SportDiscus, over 145 studies had been published on this topic. These studies provide sufficient data to permit the completion of meta-analyses that seek to quantify the direction and magnitude of association between physical activity and cancer survival.

The relationship between physical activity and survival outcomes following cancer has been most commonly investigated in breast [8–49], colorectal [8, 47, 48, 50–69], and prostate cancers [47, 48, 70–79] and all cancer sites combined [7, 8, 47, 48, 69, 79–117]. Nonetheless, in more recent years, findings from studies involving other single cancer sites, including bladder [79, 118], brain [79], childhood [119], esophagus [47, 79, 120, 121], female reproductive (endometrial, ovarian, and cervical) [47, 48, 79, 122–129], glioma [130], head and neck [47, 79], hematologic (leukemia, lymphoma, myeloma, and other hematopoietic cancers) [69, 79, 80, 131–134], kidney [79, 135], liver [8, 47], lung [8, 47, 69, 79, 80, 136, 137], melanoma [138], pancreatic [47, 69, 79, 80, 139–142], and stomach [47, 69, 79, 80, 120, 121] cancers, have also been published. Data collected for these analyses have most commonly been derived from prospective follow-up of cohorts of cancer cases identified either in case-control or cohort studies. There were also four randomized controlled exercise intervention trials that conducted long-term follow-up of trial participants for mortality outcomes [32, 33, 49, 132].

Summary of the Study Designs and Methods

Of the 145 studies published to date, cohorts from mostly developed countries have been investigated and include North America (Canada, Puerto Rico, and the USA), Europe

(Denmark, Finland, Germany, Italy, the Netherlands, Norway, Scotland, Sweden, Switzerland, the United Kingdom,) Australia/New Zealand, and Asia (China, Japan, Korea, Taiwan, Thailand, and Singapore). Contributing sample sizes varied widely, ranging from 103 to 1,290,000, as did the timing and method by which physical activity was assessed and reported before or after a cancer diagnosis. Only a few studies included repeated assessments that covered both pre- and post-diagnosis periods. The methods for assessing physical activity included self-administered physical activity questionnaires, interview-administered questionnaires, or direct measures of activity through accelerometers or exercise logs/diaries (used in the randomized controlled intervention trials); the majority relied on data from one of several self-administered physical activity questionnaires. In addition, 21 studies examined cardiorespiratory fitness (a potential surrogate measure of physical activity) and its association with cancer survival [7, 110, 114, 143–160]. The type of physical activity measured was primarily recreational activity or total physical activity, with a minority of studies assessing occupational and household activities as separate domains in addition to recreational activity. For most studies, the frequency, intensity, and duration of activities were assessed which permitted an estimation of the total energy expenditure in MET-hours/week. Overall, there is clear heterogeneity in the methods used for physical activity assessment, which needs to be considered when assessing findings derived from these studies.

Evidence Synthesis Methods

We used random effects DerSimonian and Laird models to assess the strength of the associations between physical activity and cancer survival for these studies. Specifically, we estimated the associations by time period of physical activity assessment (pre- or post-diagnosis) and by type of outcome (cancer-specific survival or all-cause mortality). For simplicity of presentation, and given the level of evidence for some cancer sites for which five or fewer studies have been published, we created five categories for the associations ranging from >20% statistically significant decreased mortality risks to >10% non-statistically significant increased risks. In addition, we examined each study to assess if the dose-response relationship between physical activity and mortality outcomes was investigated and if there was evidence of a statistically significant dose-response effect. We further reviewed the degree of consistency in the evidence across studies and categorized it as follows: (1) *yes* (with at least 10 different contributing estimates for which at least 75% had similar findings); (2) *moderate* (at least five contributing estimates with at least 75% demonstrating similar results or ≥ 10 estimates with 50–75% demonstrating similar findings); (3) *limited* (two to five contributing estimates with 75% displaying similar findings or more than five estimates with 50–75% showcasing similar findings); (4) or *no* (there was a lack of consistency (≤50% with similar findings) and/or too few estimates (i.e., only one contributing estimate) to determine consistency). These results were summarized for 18 cancer sites for which at least one study had been published that examined either pre- or post-diagnosis in association with either cancer-specific or all-cause mortality in cancer survivors (Table 3.1).

Table 3.1 Summary of the strength, dose-response, and consistency of the effects of pre- and post-diagnosis physical activity on all-cause or cancer-specific mortality outcomes by cancer site

Cancer Site	Timing of Physical Activity/Outcome	Number of studies	Strength of effect	Dose-response effect[a]	Consistency[b]
All cancers	Pre-dx: all-cause	1		0/0	No
	Post-dx: all-cause	6		2/2	Moderate
	Pre-dx: cancer-specific	33		13/17	Yes
	Post-dx: cancer-specific	4		2/2	Limited
Bladder	Pre-dx: cancer-specific	2		0/1	No
Brain	Pre-dx: cancer-specific	1		0/1	No
Breast	Pre-dx: all-cause	19		4/14	Yes
	Post-dx: all-cause	17		8/10	Yes
	Pre-dx: cancer-specific	23		0/18	Moderate
	Post-dx: cancer-specific	13		6/10	Yes
Childhood	Post-dx: all-cause	1		1/1	No
Colorectal	Pre-dx: all-cause	10		3/7	Yes
	Post-dx: all-cause	10		5/5	Yes
	Pre-dx: cancer-specific	14		3/12	Yes
	Post-dx: cancer-specific	6		4/4	Moderate
Esophagus	Pre-dx: all-cause	1		0/0	No
	Post-dx: all-cause	1		0/0	No
	Pre-dx: cancer-specific	2		0/2	Limited
Female Reproductive[c]	Pre-dx: all-cause	5		0/2	Moderate
	Post-dx: all-cause	4		0/1	Limited
	Pre-dx: cancer-specific	5		0/4	Limited
Glioma	Post-dx: all-cause	1		0/0	No
Head and Neck	Pre-dx: cancer-specific	2		0/2	No
Hematologic	Pre-dx: all-cause	3		4/6	Moderate
	Post-dx: all-cause	2		4/4	Moderate
	Pre-dx: cancer-specific	6		1/9	Yes
	Post-dx: cancer-specific	1		0/1	No
Kidney	Post-dx: all-cause	1		1/1	No
	Pre-dx: cancer-specific	2		1/2	No
	Post-dx: cancer-specific	1		0/1	No
Liver	Pre-dx: cancer-specific	3		3/4	Limited
Lung	Post-dx: all-cause	2		0/0	Limited
	Pre-dx: cancer-specific	5		4/6	Moderate
Melanoma	Pre-dx: all-cause	2		0/0	Limited
	Pre-dx: cancer-specific	1		0/0	No
Pancreas	Pre-dx: cancer-specific	8		0/10	No
Prostate	Pre-dx: all-cause	2		1/2	No
	Post-dx: all-cause	5		3/3	Moderate
	Pre-dx: cancer-specific	9		0/8	Moderate
	Post-dx: cancer-specific	4		2/3	Limited
Stomach	Pre-dx: all-cause	1		0/0	No
	Post-dx: all-cause	1		0/0	No
	Pre-dx: cancer-specific	4		2/5	Moderate

Colour Scheme	Strength of effect
	Statistically significant >20% decrease
	Statistically significant 0-20% decrease
	Non-statistically significant decrease >10%
	Null
	Non-statistically significant increase >10%

Abbreviations: *Pre-dx* pre-diagnosis, *Post-dx* post-diagnosis

[a]Dose-response: Number of estimates finding statistically significant dose-response ($p < 0.05$)/number of estimates evaluating dose-response

[b]Consistency: Established using the following criteria: (1) *yes* (with at least 10 different contributing estimates for which at least 75% had similar findings); (2) *moderate* (at least five contributing estimates with at least 75% demonstrating similar results or ≥10 estimates with 50–75% demonstrating similar findings); (3) *limited* (two to five contributing estimates with 75% displaying similar findings or more than five estimates with 50–75% showcasing similar findings); (4) or *no* (there was a lack of consistency (≤50% with similar findings) and/or too few estimates (i.e., only one contributing estimate) to determine consistency)

[c]Female reproductive cancers: Number of contributing estimates = pre-dx all-cause, endometrial ($n = 2$) and ovarian ($n = 3$); post-dx all-cause, endometrial ($n = 2$), ovarian ($n = 1$), and cervical ($n = 1$); pre-dx cancer-specific, endometrial ($n = 2$), ovarian ($n = 3$), and cervical ($n = 1$)

Overall Results

Findings presented in Table 3.1 support that the highest versus lowest levels of physical activity were associated with statistically significant decreases of >20% in cancer-specific or all-cause mortality outcomes in studies that assessed all cancer sites combined and ten other specific tumor sites, including breast, colorectal, female reproductive, glioma, hematologic, kidney, liver, lung, prostate, and stomach cancers. The strongest and most consistent evidence was observed for all cancer sites combined and breast, colorectal, and prostate cancers with data supporting an effect for all associations examined (i.e., pre- and post-diagnosis physical activity and cancer-specific and all-cause mortality).

We also examined the question of timing of physical activity in relation to mortality outcomes (Figs. 3.1, 3.2, 3.3, 3.4, 3.5, and 3.6). When all cancer sites combined,

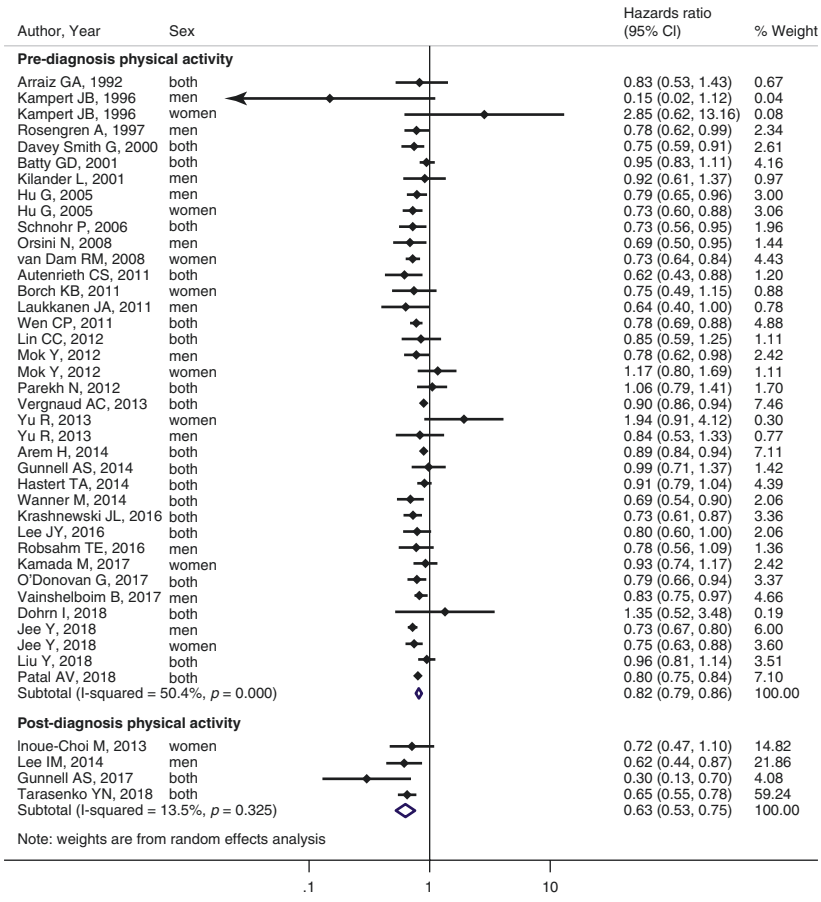

Fig. 3.1 Pre- and post-diagnosis physical activity and cancer-specific mortality for studies that combined all cancer sites

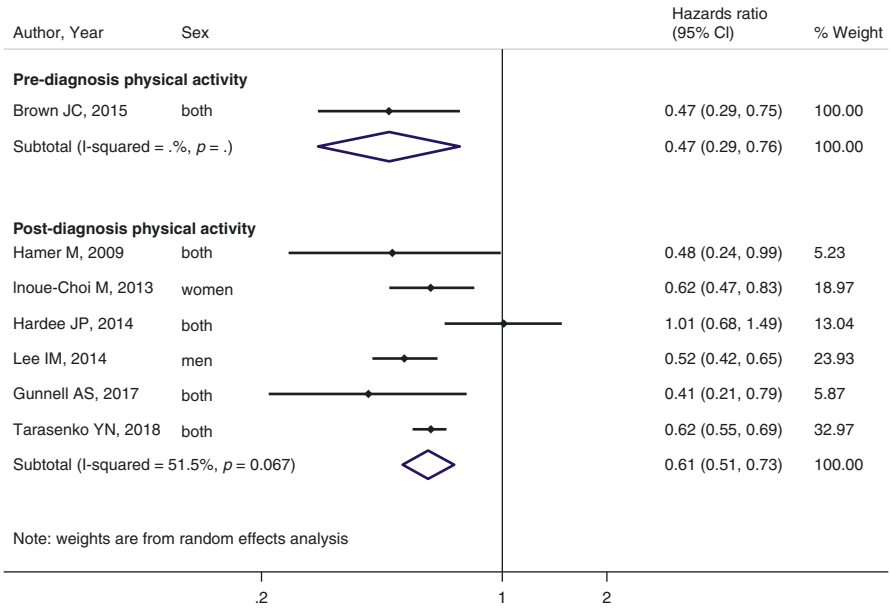

Fig. 3.2 Pre- and post-diagnosis physical activity and all-cause mortality for studies that combined all cancer sites

breast and colorectal cancers were considered, reductions in mortality risks were observed for both pre- and post-diagnosis activity. However, post-diagnosis physical activity was generally more protective (HR ~0.60) compared with pre-diagnosis physical activity (HR ~0.80) for both cancer-specific and all-cause mortality estimates.

Population Subgroups: Effects by Race

The emerging area of precision oncology has raised interest in determining whether patient sociodemographic characteristics or clinical and pathologic characteristics might predict populations or subgroups within a specific cancer population that could particularly benefit from physical activity. Unfortunately, to date, there exist only a limited number of studies available to contribute to meta-analyses that seek to evaluate the relationships between subgroups within a study population and physical activity. While this lack of evidence adversely influences the strength of statements that can be drawn from our findings, several noteworthy findings are worth consideration. First, breast cancer is the only cancer site to have investigations completed on racial subgroups [17, 23, 38, 39]. Yet the established survival disparities by race for most cancers highlight the importance of determining whether or not race is a potential effect modifier of the association between physical activity and cancer survival. Furthermore, physical activity levels and types of physical activity undertaken

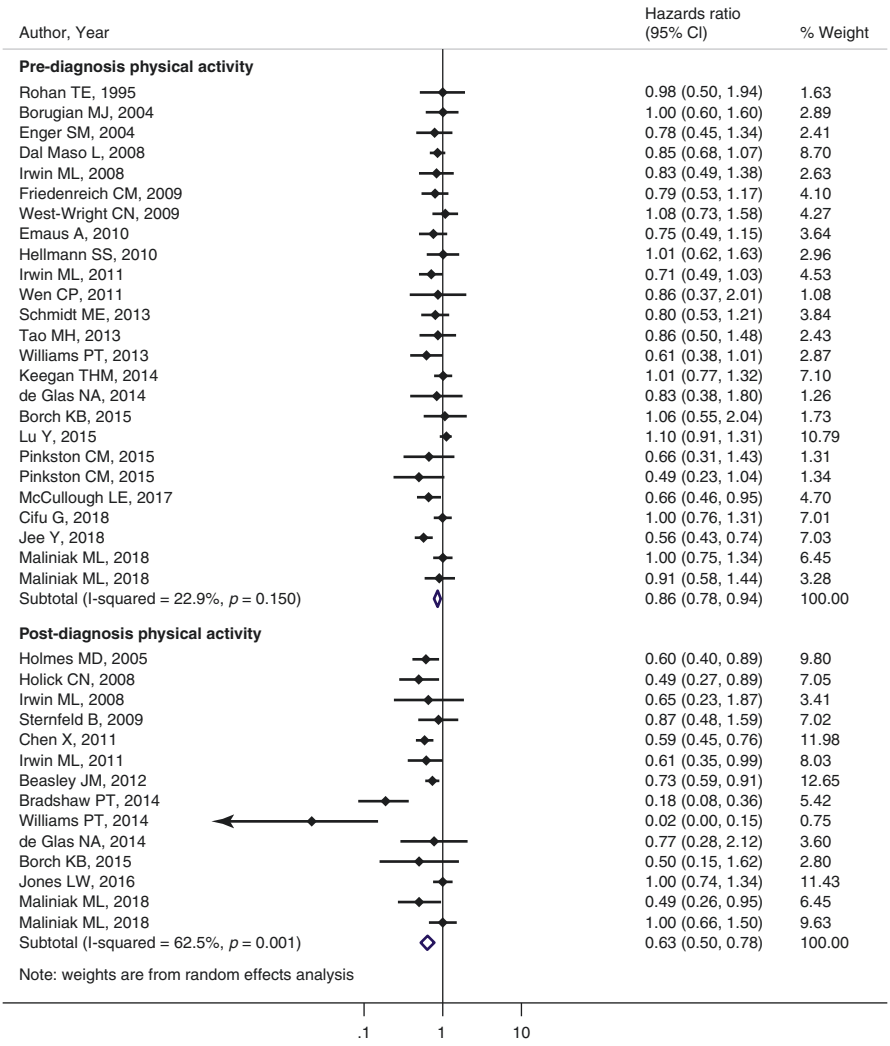

Fig. 3.3 Pre- and post-diagnosis physical activity and breast cancer–specific mortality

have been shown to differ by race. For example, African-American women are less likely to meet physical activity guidelines compared with white women; Hispanic women most frequently report walking and household activities, while non-Hispanic white women are more likely to report participation in sport-based activities [161]. Preliminary findings from our meta-analyses, using data from the few breast cancer studies that provided race-specific estimates, suggest that physical activity (pre- and post-diagnosis) is at least as beneficial for breast cancer-specific and all-cause mortality for African-American, Hispanic, and Asian-American women, as it is for white women. More data within and beyond breast cancer cohorts are required to improve the consistency and strength of these findings.

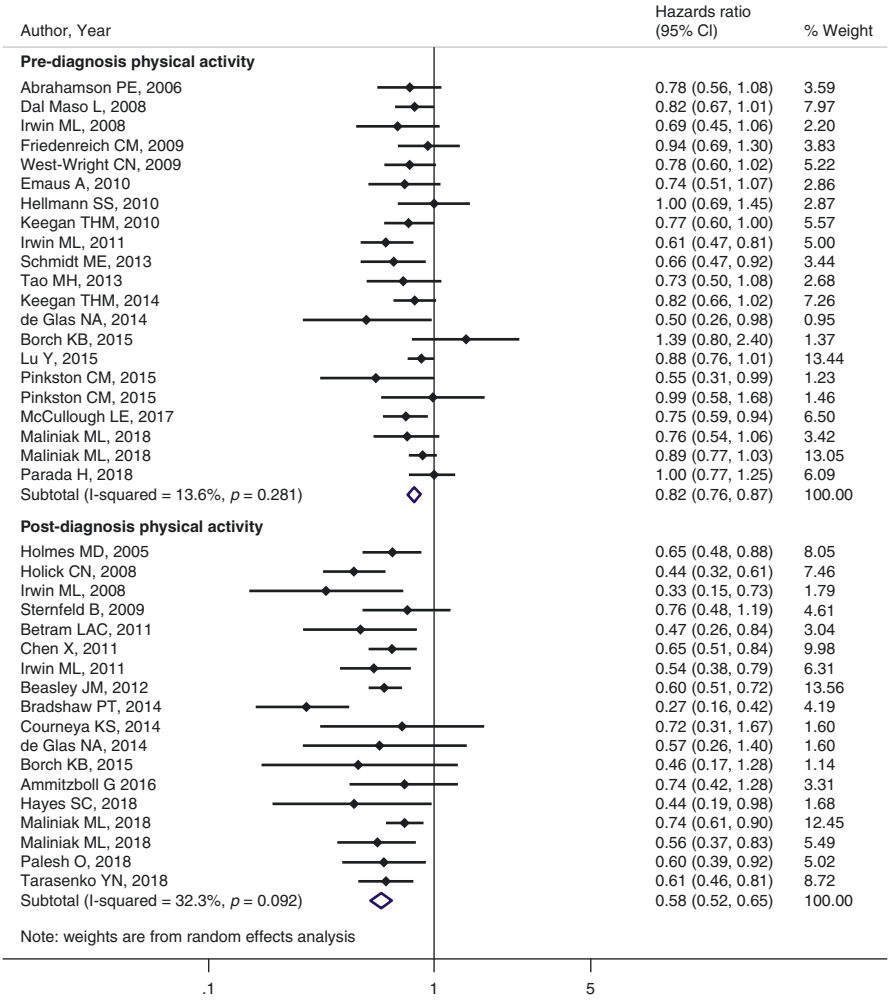

Fig. 3.4 Pre- and post-diagnosis physical activity and all-cause mortality in breast cancer survivors

Precision Oncology: Effects by Hormone Receptor Status

The differences in etiology, treatment, and prognosis for hormone receptor-positive and hormone receptor-negative cancers have also raised questions regarding the potential effect of physical activity in providing survival benefits among these subgroups [162]. Nine studies, involving women with breast cancer, presented stratified estimates for effect of physical activity by hormone receptor status [9, 13, 17, 20, 25, 29, 31, 38, 41], enabling us to explore these relationships in meta-analyses. We found statistically significant reductions of risk for both hormone receptor-positive and hormone receptor-negative breast cancers associated with

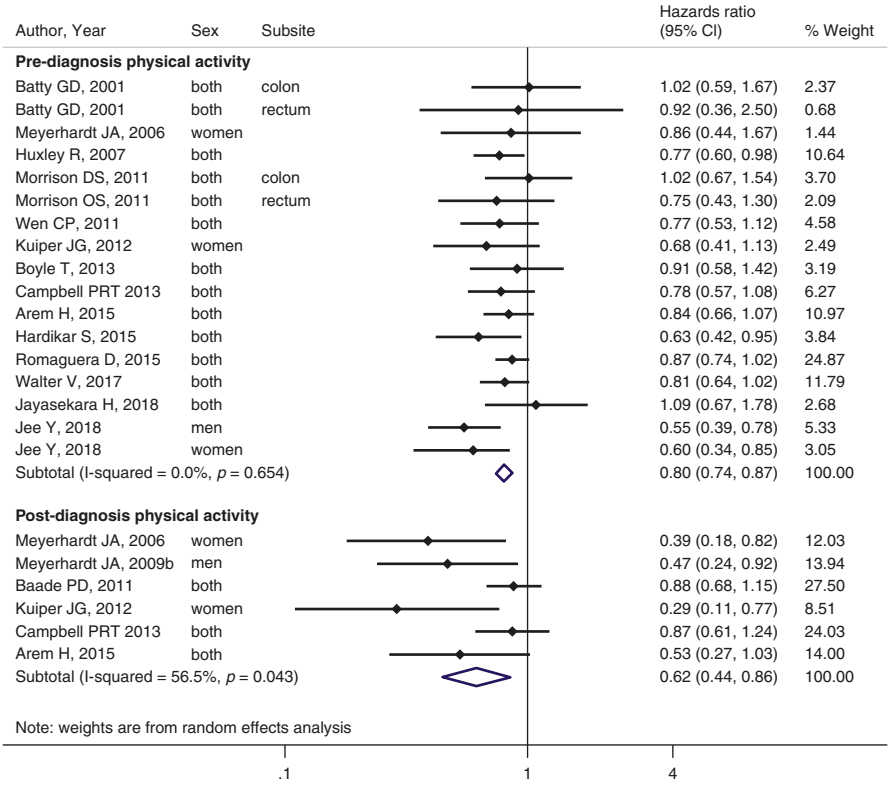

Fig. 3.5 Pre- and post-diagnosis physical activity and colorectal cancer-specific mortality

post-diagnosis physical activity and both cancer-specific and all-cause mortality outcomes (cancer-specific HR+ 0.58 (0.45–0.75), HR− 0.59 (0.42–0.83); all-cause HR+ 0.66 (0.51–0.84), HR− 0.57 (0.42–0.78)). Hence, physical activity seems to confer survival benefits regardless of hormone receptor status in breast cancer survivors. To date, there are an insufficient number of studies examining triple-negative breast cancers in association with physical activity and survival to draw any conclusions for this patient population.

Precision Oncology: Effects by Cancer Stage

Another important predictor of survival after cancer is stage at diagnosis. As such, we examined the results from studies with data stratified by stage (Fig. 3.7), with studies involving colorectal and breast cancers providing sufficient data for this analysis. No clear patterns were identified for the association between physical activity and survival. Overall, there was evidence of a risk reduction of mortality outcomes for all cancer stages, with one notable exception. Specifically, findings

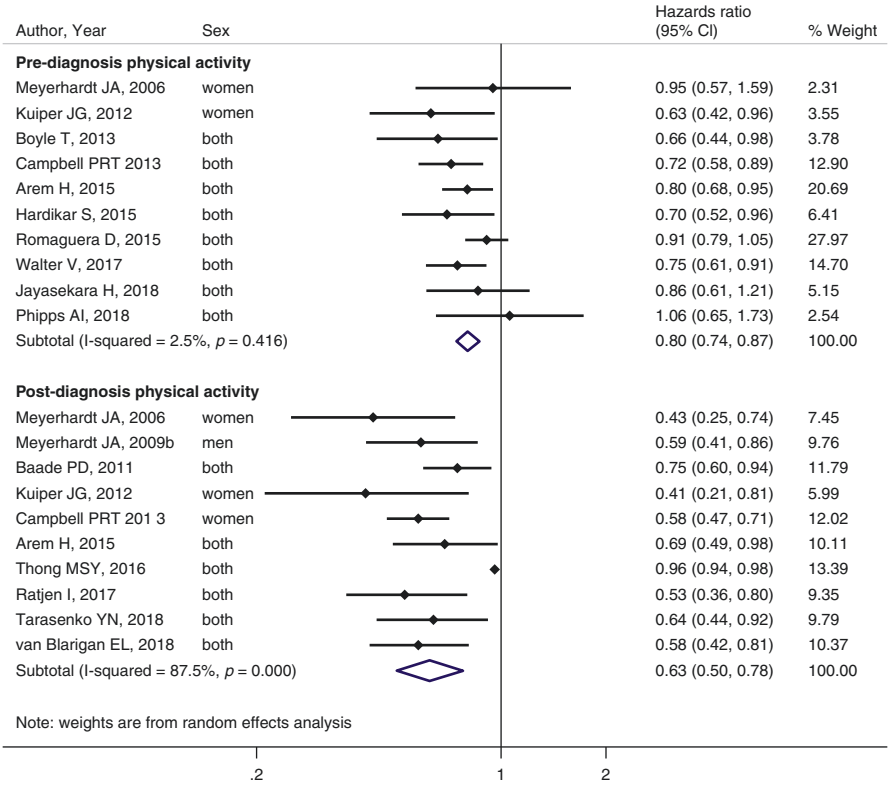

Fig. 3.6 Pre- and post-diagnosis physical activity and all-cause mortality in colorectal cancer survivors

from one colorectal cancer study with estimates for patients with stage IV disease suggested that post-diagnosis physical activity was associated with an increased risk of mortality, though this estimate should be interpreted with caution because of its small sample size and consequently wide confidence intervals.

Other important population subgroups warranting attention in future research include differences by sociodemographic characteristics and clinicopathologic characteristics, such as molecular tumor markers. To date, there have been an insufficient number of studies conducted on these population subgroups to provide any summaries.

Other Cancer Survival Outcomes and Physical Activity

While cancer-specific and all-cause mortality outcomes are the most commonly reported outcomes to consider, other survival outcomes have been investigated. For cancer recurrence or progressions, the following outcomes have been assessed: first recurrence or progression, late recurrence (>5 years), non-relapse mortality,

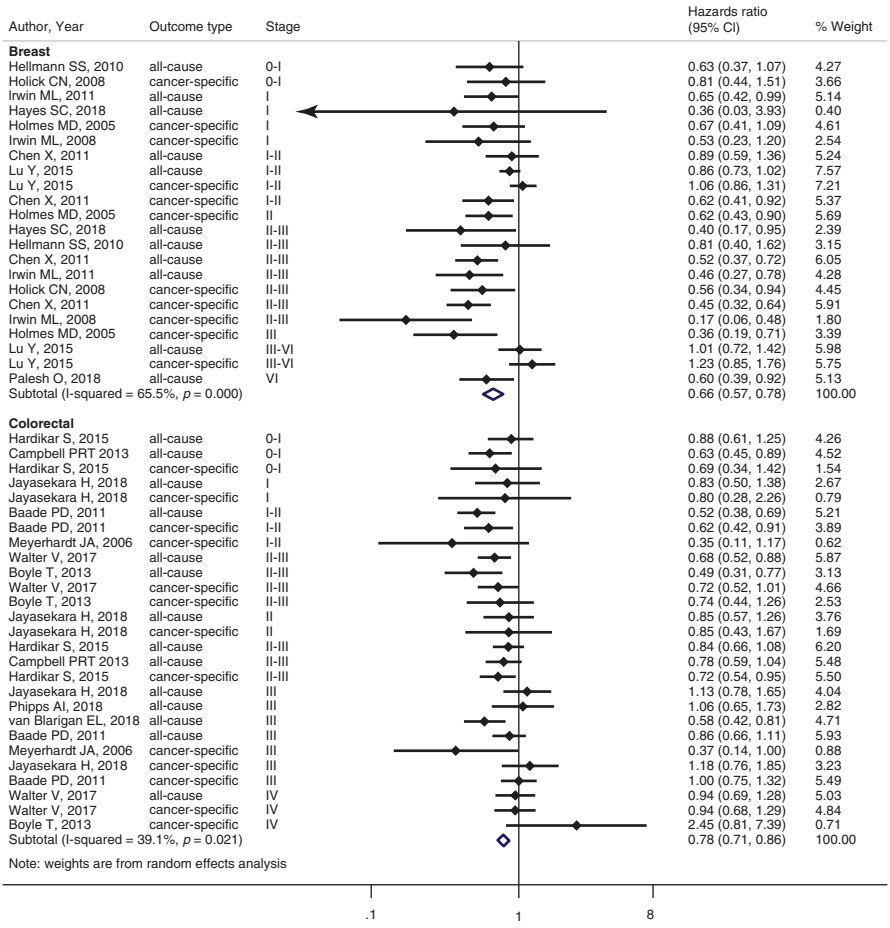

Fig. 3.7 Physical activity and all-cause and cancer-specific mortality in breast and colorectal cancer, by stage

progression-free survival, recurrence, recurrence-free interval, recurrence-free survival, progression or new primary cancer, recurrence-free period, recurrent/progressive primary cancer, relapse/disease-specific mortality, and time to recurrence. Unfortunately, the inconsistency in the definitions of these additional survival outcomes made it particularly challenging to compare findings within and between cancer sites. Acknowledging these limitations, by combining categories of first recurrence or progression, recurrence, progression or new primary cancer, and recurrent/progressive primary cancer, we found seven studies investigating the effects of physical activity (either pre- or post-diagnosis) on specifically first recurrence or progression in breast cancer [9, 13, 18, 19, 24, 28, 41], one in prostate cancer [76], and one in childhood cancers [119]. The pooled hazards ratios for each of these cancer sites are 0.90 (0.78–1.04), 1.05 (0.80–1.39), and 0.83 (0.59–1.17),

respectively. While the lack of statistical significance in these findings, alongside potential heterogeneity in the outcome measures, highlights the need for caution in interpreting these findings, it seems plausible that a trend toward a potentially protective effect of physical activity is emerging, at least in relation to breast cancer recurrence/progression. The use of standardized endpoint definitions, such as those provided by the STEEP guidelines, in future observational epidemiologic studies would facilitate future and important summaries [163].

Change in Physical Activity and Cancer Outcomes

Following a diagnosis of cancer, patients are often motivated to seek out and implement positive changes to their behavior, for multiple reasons, which include to improve coping, rehabilitation, quality of life, and survival [164]. From a public health and patient perspective, it would be particularly useful to understand whether or not changes in physical activity from pre- to post-diagnosis also influence survival. We found nine studies that reported on the relationship between physical activity changes and cancer-specific or all-cause mortality in cancer survivors, with either "unchanged levels" or "inactive" defined as the reference category for comparisons across subgroups [17, 26, 50, 53, 74, 76, 126, 134, 135]. Overall, increasing physical activity from pre- to post-diagnosis levels was associated with decreased risk of mortality (HR, 0.79, 0.69–0.92). When stratified by type of survival outcome (all-cause and cancer-specific mortality), results remained relatively unchanged for all-cause mortality (HR, 0.76, 0.64–0.90), but the magnitude of effect was attenuated, and the estimate was no longer statistically significant for cancer-specific survival (HR, 0.84, 0.65–1.08) (Fig. 3.8). These results indicate that increasing physical activity levels post-diagnosis, irrespective of meeting levels consistent with physical activity guidelines, may have positive effects on survival. However, the heterogeneity which exists relating to the method of determining physical activity changes (including differences in what constitutes a change and timing of the change) highlights the need for caution in interpreting statistical significance and clinical relevance of findings, as well as the need for more research in this area.

Resistance Training and Cancer Survival

The studies included in this review have primarily examined the effects of aerobic physical activity or total physical activity on survival outcomes in cancer populations. Despite the more recent inclusion of resistance exercise in physical activity guidelines for people with cancer [1], there is limited information pertaining to the effect of resistance training, or muscle-strengthening activity, on survival outcomes in cancer populations. Specifically, six studies identified in our review assessed this association in populations consisting of all cancer survivors, as well

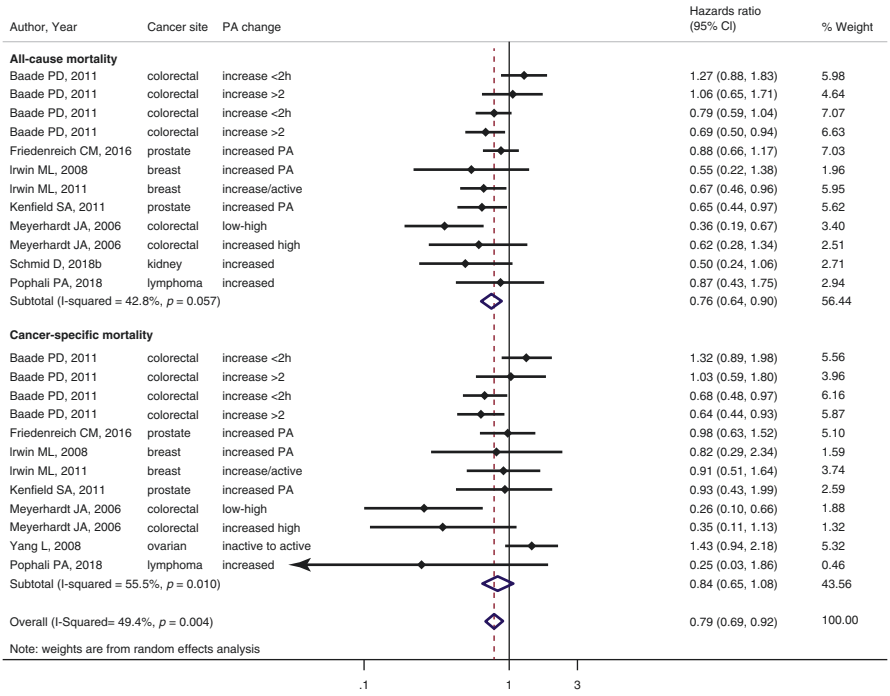

Fig. 3.8 Forest plot of increases of physical activity from pre- to post-diagnosis related to all-cause and cancer-specific mortality

as independently for colorectal, breast, endometrial, and prostate cancer survivors (Table 3.2) [48, 56, 100, 102, 108, 112]. These studies varied in their definitions of participation in muscle-strengthening activities from assessing lifetime resistance training as a dichotomous variable of yes versus no to assessing if participants met the strength training guidelines. Overall, while there was a trend, based on effect size for decreases in both all-cause and cancer-specific mortality outcomes, for cancer survivors who reported engaging in the highest versus lowest categories of strength training (HR range, 0.46–1.15), however, confidence intervals often crossed the null value. Of particular note are findings derived from a cancer cohort study that compared individuals who met neither aerobic nor muscle-strengthening guidelines to individuals who met either one or both guidelines [48]. Results suggested that meeting both strength training and aerobic activity guidelines had a compounding effect, wherein stronger improvements in survival were observed when both components of physical activity guidelines are met, compared to when only one component of guidelines is met. These represent important findings, particularly relevant to physical activity guidelines promoted to those with cancer, but also require confirmation in future epidemiological and clinical trial research. Since there is currently only one study that we identified which investigated the compounded effect of meeting both aerobic and strength training physical activity guidelines, future

Table 3.2 Summary of six studies investigating the effect of muscle-strengthening exercises on mortality outcomes in cancer survivors

First author, year, country	Study name/ description	Sample size	Cancer type	Muscle-strengthening definition	Results
Boyle et al. 2013, Australia [56]	The Western Australia Bowel Health Study	879	Colorectal cancer	Lifetime resistance training (definite vs. none) based on the name of activities listed on physical activity questionnaire	*All-cause mortality* Males: HR 0.64 (0.26–1.60) Females: HR 0.46 (0.13–1.66) *Cancer-specific mortality* Males: HR 0.81 (0.32–2.05) Females: HR 0.50 (0.14–1.84)
Yu et al. 2013, China [100]	Community-dwelling Chinese men and women aged 65 and older	2867	All cancers	The Physical Activity Scale of the Elderly (PASE). Strenuous/muscle-conditioning activity, active vs. inactive	*Cancer-specific mortality* Males: HR 0.89 (0.57–1.39) Females: HR 1.15 (0.59–2.25)
Hardee et al. 2014, USA [102]	The Aerobics Center Longitudinal Study	2863	All cancers	Participants who responded "yes" to free weights or weight training and had exercised at least 1 day per week vs. those who did not	*All-cause mortality* HR 0.67 (0.45–0.99)
Kraschnewski et al. 2016, USA [108]	The 1997–2001 National Health Interview Survey (NHIS)	30,162	All cancers	Participants responded how often they partook in leisure-time physical activities specifically designed to strengthen muscles. Categorized into whether guidelines of at least twice per week were met vs. not	*Cancer-specific mortality* HR 0.81 (0.69–0.96)
Kamada et al. 2017, USA [112]	The Women's Health Study	28,879	All cancers	Participants asked what their approximate time spent per week on weight lifting/ strength training. ≥60 minutes/week vs. 0 minutes/week	*Cancer-specific mortality* HR 0.92 (0.68–1.24)

(continued)

Table 3.2 (continued)

First author, year, country	Study name/ description	Sample size	Cancer type	Muscle-strengthening definition	Results
Tarasenko et al. 2018, USA [48]	The 1999–2009 National Health Interview Survey	13,997	All cancers and separately by breast, prostate, colorectal, and endometrial cancers	Whether participants met aerobic (≥150 minutes/week) or strength training (≥2 days per week) guidelines. Met guidelines on muscle-strengthening activities only or met both guidelines vs. met neither guidelines	*All-cause mortality: All cancers* Only muscle: HR 0.94 (0.78–1.14) Both: HR 0.60 (0.50–0.73) *Cancer-specific mortality: All cancers* Only muscle: HR 0.89 (0.63–1.25) Both: HR 0.52 (0.38–0.72) *All-cause mortality: Breast* Only muscle: HR 0.90 (0.58–1.39) Both: HR 0.72 (0.45–1.17) *All-cause mortality: Prostate* Only muscle: HR 0.96 (0.65–1.40) Both: HR 0.54 (0.34–0.86) *All-cause mortality: Colorectal* Only muscle: HR 0.87 (0.50–1.53) Both: HR 0.80 (0.39–1.66) *All-cause mortality: Endometrial* Only muscle: HR 0.48 (0.20–1.16) Both: HR 0.92 (0.40–2.10)

research is warranted to determine whether or not these findings are observed by others. Mechanistically, there is biologic plausibility for an association between strength training and improved survival. Strength training is more effective than aerobic exercise at leading to increases or preservation over time in muscle mass and strength, higher muscle mass and strength are associated with improved physical functioning and quality of life, and higher muscle mass and strength have independently been associated with improved survival [165].

Cardiorespiratory Fitness and Cancer Survival

Cardiorespiratory fitness (CRF), also known as exercise tolerance or physical fitness, refers to the ability of the circulatory, respiratory, and musculoskeletal systems to supply oxygen during sustained physical activity [166]. While higher physical activity levels have been associated with higher physical fitness, these terms are not synonymous, and it is possible that an individual may report high levels of physical activity but have low physical fitness. Consequently, exploring the relationship between physical fitness and survival outcomes following cancer is relevant. Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure [167, 168]. In contrast, physical fitness (as captured by CRF) represents the capacity to which an individual is able to achieve or perform physical activity [168]. With these distinctions made, it is important to also investigate the utility of using cardiorespiratory fitness as a predictor of cancer survival.

Schmid and Leitzmann completed a systematic review and meta-analysis on this topic in 2015 [169], which identified six studies capturing physical fitness information on 71,654 individuals and 2002 cases of total cancer mortality [7, 143–147]. From this review, these authors found that compared to low levels of cardiorespiratory fitness, intermediate levels and high levels of cardiorespiratory fitness were associated with statistically significant decreased risks of total cancer mortality (relative risks, 0.80 [0.67–0.97] and 0.55 [0.47–0.65], respectively). Several studies were not included in their review that examined total cancer mortality and cardiorespiratory fitness [110, 114, 148–155], and since publication of their review, there have been additional studies reporting on the relationship between cardiorespiratory fitness and site-specific cancer mortality [156–160]. These additional articles support and strengthen Schmid and Leitzmann's findings with growing evidence to suggest that intermediate and high levels of cardiorespiratory fitness compared to low levels of cardiorespiratory fitness are associated with survival benefits in cancer populations.

There are some limitations to this body of research, including that the majority of studies have been restricted to male samples [110, 114, 147, 149, 150, 152, 153, 155–158, 160] and that a high proportion of the published findings have used data from the Aerobics Center Longitudinal Study [153, 155, 157–160], both of which limit the generalizability of results to the wider cancer population. With these

caveats taken into consideration, the evidence does suggest that, overall, there are inverse and statistically significant associations between cardiorespiratory fitness and improved survival outcomes in cancer populations.

Exercise and Cancer Survival: Evidence from Clinical Trials Research

Besides the observational epidemiologic studies reviewed thus far, preliminary clinical trial evidence on the potential effect of participation in an exercise intervention, during or following treatment for cancer, on survival outcomes is also emerging. Data derived for these analyses have come from cohorts with breast cancer [32, 49], lymphoma, and leukemia [132, 170] and patients with bone metastasis following a range of cancers [171] (sample size range across the five trials, 60–337), with >65% of participants in all studies having completed or currently receiving chemotherapy during the intervention period. Interventions evaluated have involved aerobic-based only, resistance-based only, and aerobic- and resistance-based exercise, commencing during or post-active adjuvant therapy, with varying durations (range, 12–32 weeks) and mixed degree of supervision. Due to the small number of trials, and degree of heterogeneity between the samples and interventions evaluated, we provide here a narrative summary of the findings (rather than results from meta-analyses). A beneficial effect of exercise on all-cause mortality (HR, 0.45–0.71) was found in three of the five trials, with results remaining relatively unchanged following adjustment for other prognostic characteristics [32, 49, 132]. However, no effect of exercise on all-cause mortality (HR, 1.06 and 1.10) was reported in the remaining two trials (involving patients with metastatic disease and patients with lymphoma) [170, 171].

Comparison of findings from the two breast cancer trials warrants particular attention [32, 49]. First, sample characteristics, including age, body mass index, and stage of disease, were relatively similar between the two trials. In addition, of the five trials published to date on this topic, these two trials had the largest sample sizes (242 [32] and 337 [49]), evaluated the longest intervention (approximately 17 weeks in one trial [32] and 32 weeks for the other [49]), and longest time to follow up of survival data (89 [32] and 100 months [49]), minimizing some of the heterogeneity that would limit comparisons of findings. Further, the findings derived from these two trials for the effect of exercise on improving overall survival and disease-free survival were remarkably similar (HRs for overall survival, 0.60 [32] and 0.45 [49]; HRs for disease-free survival, 0.68 [32] and 0.66 [49]). Finally, despite the exploratory nature of the analyses undertaken (with limited power), the effect sizes observed are consistent with those observed in observational breast cancer studies, which suggest that improvements in survival of greater than 20% can be accrued through participation in physical activity post-diagnosis. These exciting, albeit preliminary, findings suggest that influencing physical activity behavior through exercise intervention may be beneficial for cancer outcomes.

Ongoing and Future Research

There is now not only a clear need for investigating causal associations between physical activity and cancer survival in adequately powered, randomized controlled trials but also the necessary evidence to support trial design, implementation, and evaluation. In addition, the recognized limitations in previous observational epidemiologic studies need to be addressed in future cohort studies. Progress in science addressing this gap is already happening. For example, the Alberta Moving Beyond Breast Cancer (AMBER) cohort study involves objective assessment of physical activity, sedentary behavior, health-related fitness, and breast cancer outcomes (target sample size, 1500) [172]. These design features address limitations of existing cohort studies evaluating physical activity and cancer survival outcomes, which have relied heavily on self-reported assessments of dose and type of physical activity, without concurrent assessment of fitness and sedentary behavior. Further, there now exist at least four randomized controlled exercise intervention trials, with target sample sizes providing adequate power for survival analyses following colon, metastatic prostate, ovarian, and allogeneic hematopoietic stem cell transplant patients [173–176]. Together these studies provide the ideal platform for improvements in knowledge needed to transform cancer care practice. Current and future research that seeks to explore optimal exercise dosage, modes of delivery, timing and duration of interventions, and characteristics that influence ability and capacity for a physiological and psychological response to exercise will ensure the workforce is equipped to prescribe evidence-based exercise to the growing cancer survivorship population.

Summary

Rapidly accumulating evidence from observational epidemiologic studies and follow-ups from randomized controlled exercise intervention trials supports recommendations to maintain and increase physical activity after cancer diagnosis for improved survival outcomes. This review found evidence for improved cancer-specific and all-cause mortality outcomes for 11 different cancer sites (10 specific cancer sites and all cancer sites combined), as well as preliminary evidence for decreased risk of recurrence and progressions. Increasing activity from pre- to post-diagnosis may also improve these outcomes after cancer. Population subgroups that might most benefit from physical activity remain unclear given the paucity of evidence to date. All stages of cancer appear to benefit equally from physical activity done either before or after cancer. More research is needed that focuses on these subgroups defined by sociodemographic characteristics as well as clinical and pathologic tumor characteristics. Additional research also needs to clarify the appropriate type, dose, and timing of physical activity that are most beneficial for improved survival outcomes by cancer site. This future research will help address the remaining gaps in understanding on the appropriate physical activity recommendations that can be provided to improve survival after cancer.

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Chapter 4
Mechanisms of Exercise in Cancer Prevention, Treatment, and Survivorship

Hannah Savage and Keri L. Schadler

Introduction: Physical Activity and Cancer

It is well established that maintaining a healthy lifestyle which includes regular physical activity reduces the risk of developing numerous types of cancer, including breast, prostate, colon, and kidney cancers. The evidence for the relationship between higher physical activity levels and reduced risk of developing these cancers is strong, based on large datasets and meta-analyses, and has been extensively reviewed [1–3].

Similarly, there is strong meta-analysis-level data supporting a relationship between increased physical activity and decreased risk of death from cancer even after cancer occurs. Evidence also suggests that while exercise appears to reduce the overall risk of developing and dying from cancer, the effect of exercise within cancer types is nuanced and may have disproportionate impact on specific molecular subtypes of broader cancer diagnoses. For example, in a 26-year study of 49,160 men measuring the relationship of physical activity to prostate cancer development, men in the highest quintile of exercise intensity had a 30% lower risk of

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developing an advanced cancer and 25% lower risk of lethal cancer in comparison to men in the lowest quintile [4]. Interestingly, men in the top quintile of amount of vigorous exercise had a 29% lower risk of TMPRSS2:ERG fusion-positive, but no difference in the risk of fusion-negative, prostate cancer compared to men in the lowest quintile [4].

Similarly, in a study examining physical activity and the risk of colorectal (CRC) or colon cancer in 2769 Korean individuals, regular exercise significantly decreased the risk of CRC or colon cancer [5]. For CRC, the presence of a PITX1 minor allele confers higher risk. In this study, a significant interaction effect between exercise, the presence of the PITX1 minor allele, and the risk of CRC or colon cancer was identified. Individuals with the PITX1 minor allele who did not exercise regularly were at the highest risk of developing CRC and colon cancer, leading the authors to conclude that particularly for individuals with the PITX1 minor allele, physical activity is important.

Another example of a differential impact of exercise in patients with varying molecular subtypes of tumors was demonstrated in 803 Caucasian bladder cancer patients and 803 healthy controls [6]. This study evaluated both risks associated with behavior, such as low, medium, or high physical activity, and genetic polymorphisms of the mTOR pathway that increase the risk of bladder cancer. The low- or medium-activity groups had a significantly higher risk than the high-activity group of developing cancer independent of genotype. Interestingly, when stratified by genotype (based on the number of single nucleotide polymorphisms in the mTOR pathway), a low activity level correlated with a 2.74-fold increased risk for a low-risk genotype, a 3.72-fold increased risk for a medium-risk genotype, and a 3.45-fold increased risk for a high-risk genotype, indicating that physical activity may be most beneficial for persons with the medium-risk genotype [6].

These studies and others support the need for understanding the cellular and molecular mechanisms by which exercise modulates cancer development, as the most appropriate exercise interventions are unlikely to be “one size fits all” either as a preventive or therapeutic method. The studies discussed above and several others indicate that tumors which are driven by specific genetic mutations may respond differently to exercise than those driven by others, suggesting that the mechanism of action of certain exercise interventions may be dependent on molecular pathways that are also important in cancer development. Identification of the mechanisms by which exercise impacts tumor biology and the molecular contexts in which exercise is most effective is necessary to achieve the most beneficial prescriptive exercise interventions for the prevention, treatment, and survivorship of cancer. Several of the mechanisms by which exercise impacts cancer were recently reviewed [7]. In this chapter, we add to the existing review literature on what is known about the mechanisms by which exercise modulates cancer. Mechanisms to be discussed include changes to the tumor vasculature and epigenetic regulation (Fig. 4.1) as well as changes to the immune system and circulating factors (Fig. 4.2).

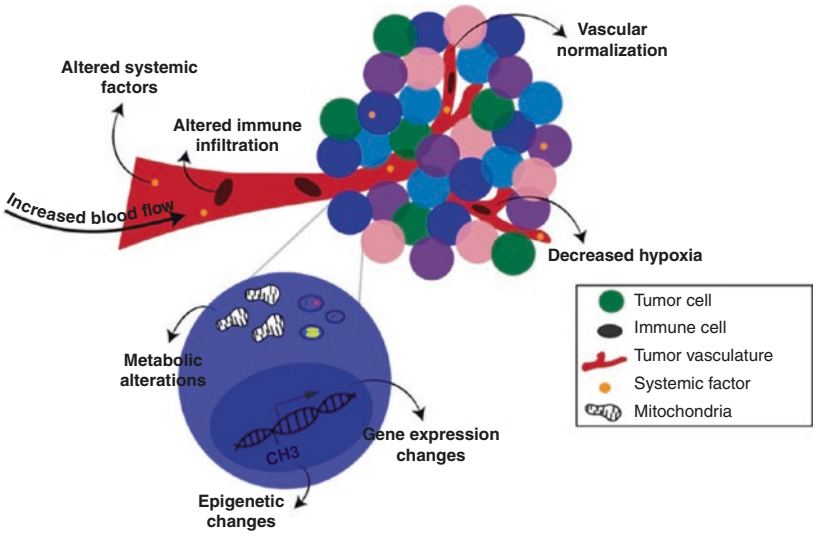

Fig. 4.1 Mechanisms of exercise impacting the tumor cells and tumor microenvironment**.** Exercise may impact tumor growth by altering tumor vasculature, by inducing epigenetic changes within tumor cells or cells of the microenvironment, or by inducing changes in local immune cell infiltration and activation

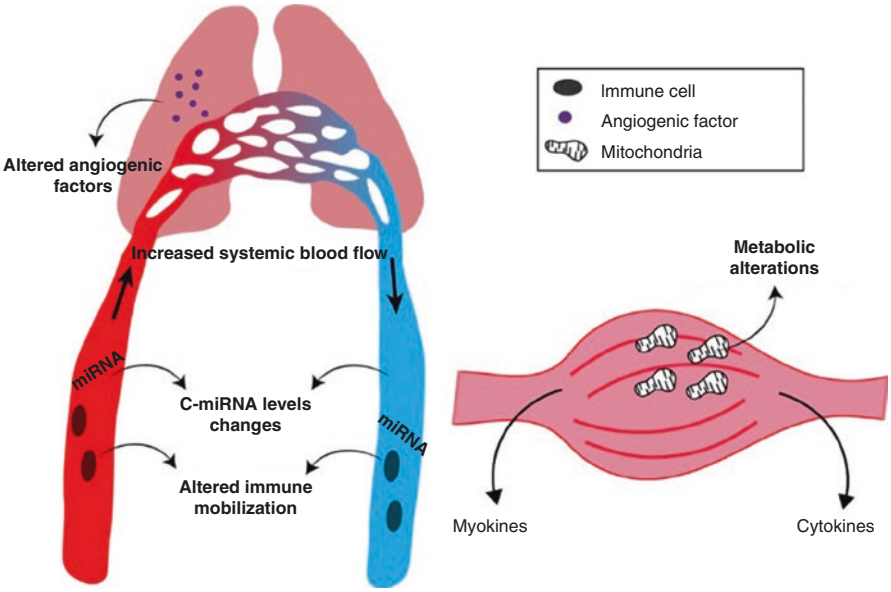

Fig. 4.2 Systemic changes due to exercise may impact tumorigenesis and tumor growth . Exercise may impact tumor growth by inducing changes in circulating myokines, cytokines, or angiogenic factors, by changing the number or type of immune cells in circulation, or by changing circulating miRNAs

Exercise and Tumor Vascular Function

One hallmark of cancer is the ability of the tumor to induce angiogenesis [8]. The formation and function of vasculature are largely regulated by the balance of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), and antiangiogenic growth factors, such as thrombospondin-1 (TSP-1). In general, tumor cells secrete more pro-angiogenic than antiangiogenic factors. Due to secretion of pro-angiogenic factors by tumor cells, tumors are able to induce endothelial cell proliferation and the rapid development of blood vessels by sprouting from existing vasculature, recruitment of local vasculature, and recruitment and proliferation of endothelial and perivascular progenitor cells. While inhibiting the ability of the tumor to form blood vessels with the aim of "starving" the tumor of nutrients and oxygen does work in some tumors such as renal cell carcinoma, clinical evidence suggests that pharmacologically targeting one pro-angiogenic factor is rarely sufficient for a sustained vascular inhibiting effect in patients [9]. Further, in recent years, tumor cells have been demonstrated to be able to survive extreme hypoxia, and evidence suggests that enhancing tumor hypoxia (starving the tumor of oxygen by eliminating blood supply) may actually increase the metastatic potential of tumor cells [9, 10]. Thus, the field of tumor angiogenesis has evolved in ways that are important to note prior to interpreting data on how exercise impacts tumor vasculature.

Tumor vasculature is inherently dysfunctional and inefficient due to the rapid proliferation of endothelial cells causing disorganized vasculature without appropriate hierarchy or perivascular cell coverage. In the last two decades, the concept of normalizing tumor vasculature to enhance delivery of therapeutic agents and reduce tumor hypoxia has emerged [11, 12]. Tumor vascular normalization refers to making tumor vessels more like "normal" organ vasculature, i.e., become more organized, have less sprouting and reduced proliferation, have better pericyte coverage, become appropriately permeable, and, importantly, have increased function. In this model, increasing blood flow to the tumor is beneficial because increased blood delivery to the tumor would reduce hypoxia and increase the delivery of therapeutic agents. As the impact of exercise is evaluated in regard to the tumor, it must be considered in context: treatment of some tumors would benefit from ablation of angiogenesis (ovarian cancer, renal cell carcinoma), which would be indicated by reduced microvessel density within the tumor, while treatment of most others would benefit more from tumor vascular normalization, indicated by changes to vessel structure and increased function, as an adjuvant to therapy.

Preclinical Evidence: Exercise and Tumor Vasculature

Overwhelmingly, current evidence in preclinical animal models suggests that exercise remodels tumor vasculature to improve vascular function and blood flow to the tumor. However, evidence is limited to less than 20 studies with wide variability in study design and analysis methods.

In contrast to more recent studies examining tumor vasculature and exercise which use moderate exercise doses, evaluation of blood vessels in one model of EL4 lymphoma growth in mice suggests that exhaustive high-intensity exercise (20–40 m/min for 3 h or until exhaustion daily) significantly decreased the vascular density of tumors compared to those in sedentary mice [13]. Exercise was begun on the day of tumor inoculation and caused a delay in time to peak tumor size but no change in final peak tumor size. Similar effects on microvessel density were found within hepatocellular carcinoma tumors in a study using a more moderate exercise intervention (treadmill, 60 minutes per day, 5 days per week). Microvessel density was decreased by moderate exercise in rats when exercise was initiated 6 weeks prior to and continued 4 weeks following tumor implantation [14]. The decrease in microvessel density did not correlate with a change in tumor size, but tumors from exercised rats had less viable and more necrotic tissue. In both of these studies, exercise caused decreased microvessel density but had little or no antitumor effect. Also in both of these studies, microvessel density was the only vessel analysis; other aspects of vascular structure and function were not evaluated.

Microvessel density is difficult to interpret in the absence of other features of the vasculature, as hyper-proliferation of dysfunctional vessels is not likely productive in terms of blood delivery. In contrast to the above studies, microvessel density within orthotopic breast tumor models has been shown to be increased by voluntary wheel running [15] and to be unchanged in melanoma or prostate tumor models by treadmill exercise [16]. These studies and others used multiple measures of tumor vascular structure and function to demonstrate increased blood vessel function within tumors, as discussed below.

A beneficial effect of exercise against tumor growth, and in improving blood delivery to tumors, has been consistently shown in murine and rat models of orthotopic breast cancer. Power Doppler imaging of in vivo blood flow within carcinogen-induced mammary tumors in rats demonstrated that 35 weeks of moderate-to-high-intensity treadmill running for 5 days per week led to a significant increase in blood perfusion within tumors [17]. Similarly, voluntary wheel running increased the number of functional, perfused vessels and the total blood perfused tumor area relative to sedentary controls in mammary MDA-MB-231 tumors in mice [18]. Further studies of breast tumor vascularity using 4 T1 and E0771 mammary tumor murine models confirmed that voluntary wheel running, begun at the time of tumor inoculation, positively impacts tumor vascular function [15]. In these studies, exercise conferred a significant decrease in tumor hypoxia and an increase in pericyte coverage of tumor endothelium, indicative of more functional blood vessels.

Consistent with a model in which exercise improves tumor vascular function allowing for better delivery of chemotherapy, 4 T1 mammary tumors in mice treated with exercise combined with cyclophosphamide were significantly smaller than tumors in mice treated with cyclophosphamide alone [15]. While the exact molecular response to exercise that induces tumor vascular remodeling is not yet clear, changes in breast cancer cell-secreted angiogenic factors in response to exercise have been demonstrated. For example, 8 weeks of endurance treadmill exercise

decreased IL-6 and VEGF within MC4L2 mammary tumor in mice [19]. Thus, exercise may cause the tumor itself to change the way it crosstalks with endothelial cells, leading to changes in tumor vasculature.

In a series of elegant studies utilizing orthotopic prostate tumors (Dunning R-3327 AT-1 cells implanted into Copenhagen or nude rats), exercise was demonstrated to increase blood flow to the tumor [20, 21]. Five days per week of low-to-moderate-intensity exercise (15 m/min, 60 min per day) increased blood flow to the tumor by ~200%, significantly increased the number of patent vessels (vessels delivering Hoechst 33342), and significantly decreased hypoxia *during* exercise [21]. This was attributed, in part, to the lack of ability of the tumor vasculature to contract in response to exercise. For exercise to be beneficial to patients as a method to reduce tumor hypoxia and improve therapeutic delivery, there must be some sustainable change to blood delivery to the tumor that remains *after* exercise. Indeed, 7 weeks of exercise training afforded a twofold increase in microvascular PO_2 and significantly reduced hypoxia even 48 h after exercise, suggesting that exercise caused a semipermanent improvement in blood delivery to the tumor [20].

In agreement with the studies discussed above, exercise has also been shown to improve blood vessel structure in subcutaneous melanoma and pancreatic ductal adenocarcinoma tumors. Five days per week of moderate treadmill running significantly increased the number of open vessel lumens and the average vessel length, consistent with vascular normalization. Pancreatic ductal adenocarcinoma tumors from exercised mice also had a ~25% increase in the number of functional blood vessels, which correlated with significantly better antitumor effect of gemcitabine when combined with exercise compared to gemcitabine treatment alone [16]. The unique contribution of this study to the field was that it demonstrated that the tumor vascular remodeling in response to exercise was due in part to the upregulation of antiangiogenic TSP-1. Exercise increased systemic circulating TSP-1, and in mice lacking TSP-1, the vascular remodeling effect of exercise and the increased efficacy of chemotherapy were significantly diminished. Further, the authors hypothesized with some supporting evidence that exercise increases TSP-1 by increasing the shear stress experienced by endothelial cells. The model presented indicates that increased shear stress led to the activation of nuclear factor of activated T cells (NFAT), a master transcriptional regulator of endothelial cell function, which induced TSP-1 transcription. Identification of the molecular pathways governing the tumor vascular response to exercise is critical if biomarkers representing the best intensity and duration of exercise to improve drug delivery are to be developed.

Clinical Evidence: Exercise and Tumor Vasculature

Evidence supporting the ability of exercise to impact vascular structure in tumors in patients (as opposed to animal models) is still sparse. However, one prospective study evaluated the relationship between pre-diagnosis physical activity and

vascular morphology in prostate tumors by utilizing data from the Health Professionals Follow-Up Study, which included 571 men who developed prostate cancer [22]. Prostate tumors from men who reported their usual walking pace as brisk (3–3.9 miles per hour) prior to diagnosis (median time of assessment 14 months prior to diagnosis) had significantly more regularly shaped (perimeter^2/4 × (3.14) × area) and longer blood vessels compared to those who walked at a less brisk pace, but with no difference in microvessel density. This is consistent with what was predicted by mouse models, where vascular normalization characterized by remodeling of the structure and functional capacity of blood vessels was shown. Perhaps surprisingly, there was no association between the self-reported number of hours per week of vigorous or non-vigorous activity and the vessel parameters that were measured, which included microvessel density, vessel shape, and lumen regularity.

The impact of exercise during chemotherapy on angiogenic factors and vascular function has also been studied in women with breast cancer receiving neoadjuvant doxorubicin and cyclophosphamide [23]. Twenty women participated in a study comparing the combination of an exercise intervention consisting of three supervised cycle ergometry sessions/week at 60–100% of $VO_{2\,peak}$, 30–45 min/session, for 12 weeks with chemotherapy to chemotherapy alone. In patients who were in the exercise intervention, the number of $CD133^+VEGFR2^+$ circulating endothelial progenitor cells increased over time, while it decreased in control patients. There was also an increase from baseline to the end of the 12-week intervention in circulating placental growth factor (Plgf), a pro-angiogenic factor, and a decrease in IL-2 in patients who exercised. For both of these, patients in the control groups had changes in Plgf and IL-2 expression in the opposite direction of patients who exercised.

Physical Activity and the Immune Response

The immune response to cancer cells, and the necessity of cancer cells to evade this response, is appreciated as a critical component of disease etiology. Infiltration of T lymphocytes, NK cells, and other immune cells correlates with outcome for numerous tumor types. In addition to the endogenous immune response to the tumor, manipulation of the immune system to promote an antitumor response is now being developed as a therapy. For example, checkpoint inhibition by blockage of CTLA-4 or PD-1 allows T cells to "see" tumor cells, and CTLA-4 inhibition is FDA approved to treat metastatic melanoma, while PD-1 inhibitors are in clinical trials for multiple tumor types [24, 25]. Finally, cell therapy, such as delivery of chimeric antigen receptor T cells (CAR-T) or NK cells, is also a growing field of immunotherapy [26, 27]. As immunotherapy grows to be a central component of the arsenal of cancer-targeting tools, the impact of exercise on the immune system cannot be ignored.

Exercise has long been known to regulate immune cell proliferation, migration, and function. Over the last two decades, the impact of exercise on the immune

system in the context of cancer has been explored. A number of well-written reviews on the topic exist [28–31]. There is wide variability in study outcomes depending on the duration, intensity, and type of exercise and depending on whether acute or chronic exercise was evaluated. Common themes are that exercise activates natural killer (NK) cells and T lymphocytes, increases the number of circulating immune cells acutely, may promote polarization of macrophages, and regulates the level of numerous circulating cytokines.

In healthy individuals, exercise is well known to promote lymphocytosis, an increase in the number of circulating lymphocytes. Exercise intensity is correlated to both the magnitude of lymphocytosis and to changes in the function of circulating immune cells [32]. Also in healthy individuals, there is substantial evidence for an inverse relationship between physical activity and natural killer (NK) cell function. For example, in a study of 12,014 healthy participants, physical inactivity correlated with a significantly decreased interferon gamma (IFN-γ) production by NK cells in response to stimulation relative to minimally active or active individuals [33]. In another study, serum from participants who exercised for 1 hour was shown to increase NK cell cytolytic activity in vitro, and this was correlated with low cortisol and high IFN-γ [34]. Due to the clear role of exercise in modulating the immune system in healthy people, exercise is generally expected to promote an anticancer immune response. Below we discuss evidence in support of this possibility.

Preclinical Evidence: Exercise and Immune Response to Cancer

Preclinical mouse and rat cancer models have begun to define the role of exercise as an immune modulator for cancer prevention and therapy. One of the first preclinical studies examining the impact of exercise on immune cell infiltration into tumors utilized EL4 lymphomas in BALB/c mice and exhaustive daily exercise (described previously). This study demonstrated that exhaustive exercise reduces the number of neutrophils and macrophages that infiltrate a developing tumor while increasing the number of lymphocytes in the tumor [13]. This study should be interpreted with caution, as exhaustive daily exercise is unlikely to be clinically relevant. Further, there was no characterization of lymphocyte subtypes and the increased lymphocyte infiltration by exercise was only seen at the time of peak tumor size. The current understanding of immune influences on tumor growth suggests that immune cells often play opposing roles, tumor-promoting or tumor-inhibiting, depending on their activation and/or polarization status. Thus, due to the lack of analysis of macrophage polarization (tumor-promoting or tumor-inhibiting) or lymphocyte subtype, it's not clear whether the immune cell infiltration that correlated with exercise in this study was responsible for the observed delay in time to peak tumor size.

In a work that did attempt to evaluate changes in immune cell function, rats underwent an anaerobic exercise intervention of weighted swimming intervals 4 days per week for 6 weeks prior to inoculation of Walker 256 tumor cells,

continuing until the end of the experiment [35]. Exercise significantly reduced final tumor volumes, and gut-associated lymphocytes from exercised mice proliferated significantly more in response to stimulus than lymphocytes from non-exercised mice. Further, the phagocytic capacity of gut-associated macrophages from exercised tumor-bearing rats was significantly higher than the phagocytic capacity of macrophages from non-exercised rats. This study is noteworthy in that it uses a relatively unique exercise intervention of weighted swimming and evaluates macrophage function [35].

In addition to changes in ex vivo function, as evaluated in the study of rats discussed above, changes in the phenotype (which implies changes in function) of tumor-infiltrating immune cells in response to exercise are also important to evaluate. The impact of 6 days per week, 1 h per day at 15 m/min treadmill running over a 12-week period on colon polyp development was recently examined using the ApcMin/$^{+}$ mouse model [36]. This model lends itself to the study of the impact of exercise on the immune system in the context of tumor development because the autochthonous tumors occur over time due to the genetic background of the mice and because the mice are fully immunocompetent. Mice that exercised had fewer large polyps, and mRNA analysis of mucosal tissue of the colon demonstrated fewer macrophages, both M1 and M2 phenotypes, within polyps of exercised mice. Further, tissue from exercised mice had significantly more CD8^{+} and fewer Foxp3^{+} T cells as determined by mRNA. As Foxp3 is an indicator of Treg cells, which are immunosuppressive, a reduction in this cell population may contribute to the antitumor effect of exercise.

In agreement with the above study noting fewer tumor-infiltrating macrophages, fewer CD68^{+} macrophages and fewer CD209^{+} dendritic cells were found in circulation of exercised mice after exposure to N-nitroso-diethylamine (DEN), which causes liver cancer development, compared to control [37]. In this study, mice performed 6 weeks of wheel running prior to DEN inoculation. Interestingly, the protective effects of exercise against inflammation were sex specific, as the reduced circulating innate immune cells were only observed in female mice. Female exercised mice also had a significantly smaller spike in TLR9, which activates the innate immune system, compared to female non-exercised mice. This is important as TLR9 promotes an inflammatory response, and inflammation is believed to be an early initiating step of HCC.

The NK cell response to exercise in the context of cancer has also been evaluated. In a thorough and elegant investigation of the role of NK cells in exercise-mediated tumor growth inhibition, Pedersen et al. used five different tumor types (B16F10 melanoma subcutaneous and tail vein-induced lung tumors, diethylnitrosamine-induced liver tumors, Lewis lung carcinoma, and Tg(Grm1)EPv spontaneous melanoma) to demonstrate that wheel running, particularly when initiated prior to tumor inoculation, reduces the incidence and growth rate of tumors [38]. Microarray analysis of B16F10 melanoma tumors from control or exercised mice demonstrated that 52% of upregulated genes were related to immune function and inflammation. Surprisingly, within the tumor, there was upregulation of

cytokines and immune cell markers considered to be tumor promoting (i.e., IL-10 and FoxP3) and tumor suppressing (i.e., TNF-α and NKp46), further supporting the concept of a complex immune response to exercise in the context of cancer. Despite this, the authors demonstrated significant upregulation within the tumor of several NK cell-recruiting or NK cell-activating factors (NKG2D, MULT1, H60a, Clr-b) and were able to show a clear role for NK cells in the antitumor effect of exercise. The number of tumor-infiltrating NK cells in the B16F10 melanoma model inversely correlated with tumor burden, and depletion of NK cells completely abolished the protective effect of exercise. In addition, this study provides convincing evidence that epinephrine and IL-6 upregulation by exercise promoted recruitment of IL-6-responsive NK cells to the tumor [38].

In addition to evaluation of changes in numbers of circulating or immune cells, several studies have evaluated changes of cytokines in circulation or in tumor tissue in response to exercise. Exercise is well known to change the secretion of cytokines by muscles, known as myokines, and has been shown to change cytokines such as IL-6, IFN-γ, and IL-10 [39–41]. In general, it appears that Th1-type cytokines such as IL-6 increase immediately following exercise and in some cases persist, while other cytokines, such as MCP-1, spike temporarily followed by a decrease to lower than pre-exercise levels. Unfortunately, it is difficult to identify a clear pattern of cytokine response to exercise largely due to disparate findings following widely variable exercise protocols and cytokine measurement protocols.

Notwithstanding the caveats expressed above, preclinical models utilizing tumor-bearing mice indicate that exercise likely changes the cytokine milieu systemically and within the tumor microenvironment and that these changes likely support an immune response against the tumor. An interval treadmill training intervention initiated 6 weeks prior to tumor inoculation and maintained for 6 weeks after demonstrated significant changes both within 4 T1 mammary tumors and in the spleens of mice. Tumors from exercised mice had significantly increased oncostatin M and TNF-α, but significantly decreased IL-4, relative to tumors from non-exercised mice [42]. Similarly, splenocytes from exercised mice had significantly higher IFN-γ and lower IL-4 than splenocytes from control mice. Oncostatin M has been demonstrated to be secreted by muscles and to induce apoptosis of breast cancer cells in vitro, and IFN-γ and TNF-α both promote antitumor responses. Of note, there was no difference in tumor growth between exercised and control mice in this study [42], suggesting that modulation of these cytokines alone is not sufficient to confer suppression of tumor growth.

Clinical Evidence: Exercise and the Immune Response

As predicted by animal models, exercise appears to increase the immune response in cancer patients, though the data is sparse compared to studies in healthy persons. In one recent study of breast cancer survivors, the impact of an acute bout of

exercise on circulating NK cells was examined. The study included 18 women, 9 breast cancer survivors within 3–6 months posttreatment and 9 healthy controls. Cancer survivors had lower numbers of NK cells at baseline. Thirty minutes of moderate aerobic exercise significantly increased the number of circulating NK cells in both survivors and control subjects, although the increase was not as substantial in breast cancer survivors as in control subjects [43]. In this study, the number of circulating NK cells returned to baseline in both groups within 24 h of the exercise bout. In a separate study, chronic resistance exercise in breast cancer survivors (n = 20 resistance training, 19 control) was examined over a 16-week training period and was not found to increase the number of NK or NKT cells. However, resistance training did reduce the expression of pro-inflammatory TNF-alpha by both NK and NKT cell populations compared to baseline and relative to breast cancer survivors in the control group [44]. While together this data suggests that exercise can have beneficial effects for NK cell number and function in cancer survivors, the low number of study participants and few total number of studies indicate that conclusions should be drawn with caution and further study is warranted.

It is unclear whether these findings in long-term survivors can be extrapolated to breast cancer patients still undergoing treatment, as one study found that a chronic, albeit very moderate, exercise intervention did not increase circulating immune cells. The impact of a walking exercise program on immune cell numbers in 20 women actively undergoing chemotherapy treatment demonstrated that a 12-week walking intervention caused no significant increase in the number of lymphocytes, T-helper cells, cytotoxic T cells, natural killer cells, or natural killer T cells [45].

Similar to other potential mechanisms of the impact of exercise on cancer, modification of the immune response is an exciting but as of yet not fully supported potential mechanism. Further study into how exercise regulates the immune system, and how this impacts cancer development and growth, is needed and likely to be fruitful.

Epigenetic Gene Regulation by Exercise

"Epigenetics" refers to a change in gene expression without direct alteration in the DNA sequence. Epigenetic modifications can change the frequency or magnitude of transcription of the DNA without changing the genetic code. Epigenetic modification of DNA is a key regulator of gene expression during development and in the natural processes of aging. There is also a clear role for epigenetic gene regulation in cancer development. Epigenetic modifications have been shown to alter the characteristics of tumor cells that are necessary for cancer growth [8] including proliferative signaling, evasion of cell death, induction of angiogenesis, and more [46]. Epigenetic elements including DNA methylation, histone modifications, and noncoding RNAs have been implicated in cancer and have been shown to be modified by exercise [47, 48]. However, the relationship between physical activity and

epigenetic elements, and how this relationship influences cancer progression, is not fully understood. The following section will summarize important findings and current knowledge describing the role of exercise in epigenetic changes and gene regulation including alterations in DNA methylation, histone modification, and microRNA (miRNA) in cancer.

Exercise and DNA Methylation in Healthy Tissue

DNA methylation is a common epigenetic element that regulates gene expression. In mammals, methylation occurs on cytosine nucleotides in areas of the DNA called CpG sites or islands. CpG methylation in a gene promoter is associated with decreased gene expression by altering chromosome structure and preventing binding of transcription factors or recruiting gene-repressive proteins [49]. Thus, methylation can silence or reduce expression of a specific gene, altering cellular function. DNA methylation also occurs in transposable elements, including long interspersed nuclear elements (LINEs) [50]. Methylation status of LINE-1, which comprises about 17% of the human genome [51], predicts cancer risk [52–54] and is associated with health status [55].

Exercise may alter global DNA methylation patterns of LINEs or at CpG sites. Zhang et al. found that individuals aged 45–75 who were physically active 26–30 min per day (measured by an accelerometer) had significantly higher levels of global DNA methylation based on peripheral blood analysis in comparison to individuals that were active only 10 minutes or less per day [56]. This study suggested that physical activity influences global DNA methylation; however, after data was adjusted for factors including gender, age, race, and other lifestyle factors, the differences became statistically insignificant. Weak associations were still reported in certain populations, including trends of physical inactivity associating with elevated risk of global hypo-methylation in non-Hispanics, supporting further investigation of exercise effects on global DNA methylation [56]. This study also demonstrates the relationship between factors like gender or race and global DNA methylation and the need for these to be considered when studying exercise in heterogeneous populations.

In another study, healthy individuals were evaluated pre-exercise, post-acute exercise, and post-4-week chronic exercise intervention to investigate the effect of exercise on methylation of promoter CpG sites of a natural killer (NK) cell-activating gene (KIR2DS4) and an NK cell-inhibiting gene (KIR3DL1) [57]. Interestingly, after acute exercise, a decrease in methylation was observed in the activating gene (KIR2DS4 gene) which correlated with increased gene expression, suggesting activation of NK cells by acute exercise. In contrast, chronic exercise resulted in non-significant decreases in DNA methylation and no changes in gene expression of either genes. No changes in NK cell numbers were found after acute or chronic exercise. This data suggests that acute exercise affects the NK cell

population more strongly than chronic exercise, likely through modifications in promoter methylation [57]. As NK cells are an important component of the antitumor immune response and since exercise is known to mobilize NK cells, changes in NK cell activation status by exercise are likely to impact tumor growth. Studies like these demonstrate a clear role for physical activity in regulation of DNA methylation.

Exercise, DNA Methylation, and Cancer

Due to the growing amount of literature describing the dynamic regulation of epigenetic markers in response to exercise, understanding the implications of such regulation in cancer development and progression is key. There have been increasing efforts to understand the role of exercise in cancer-related DNA methylation.

Decreased levels of genome-wide methylation are often seen in cancer cells compared to normal tissue [58]. Studies defining global DNA methylation changes in cancer have revealed that exercise can change gene expression through changes in global methylation phenotype or pattern. In a study investigating changes in genome-wide methylation, levels of methylation of LINE-1, a repetitive genome element, were used as a surrogate for global methylation levels. Six hundred women at various ages with a family history of breast cancer participated in the study. Women who reported higher physical activity than the median in each age group had higher LINE-1 methylation than women below the median [59], demonstrating that exercise may reduce cancer development in part by increasing global methylation levels.

In contrast to hypo-methylation globally as represented by LINE-1 methylation, increased CpG methylation at specific sites can result in abnormal gene expression in cancer cells. In many cancers, including colorectal cancer, gliomas, breast cancer, and more, increased levels of CpG site methylation are seen in comparison to normal tissue [60]. Global CpG site methylation status has been demonstrated to be predictive in many cancer types. Specifically, CpG island methylator phenotype (CIMP) is a term used to describe tumor types with hyper-methylation at CpG sites of tumor suppressor genes or pathways, which suppresses tumor suppressor gene expression and promotes tumor development and progression [60]. It is not yet clear whether exercise influences CIMP status or reduces risk in a CIMP status-dependent way.

Apart from studies aimed at understanding broad methylation of CpG islands such as in CIMP, more focused approaches to determine mechanisms by which exercise influences specific cancer-related gene methylation have also been done. In one study, DNA methylation in prostate patient tumor samples was measured and correlated to exercise in patients with prostate cancer [61]. Self-reported levels of physical activity were used. Individuals who engaged in vigorous exercise at least once per week had a reduced chance of progression to late-stage metastatic prostate

cancer in comparison to inactive individuals. Using the analysis of DNA methylation profiles, the authors demonstrated that patients who exercised at least one time per week had lower methylation in nine CpG sites of CRACR2A gene, an important gene involved in the innate immune system, in comparison to individuals who exercised less than once per week. Decreased methylation inversely correlated with CRACR2A gene expression [61], revealing a possible mechanism by which exercise reduces the risk of prostate cancer progression through alteration of the methylation status of CRACR2A gene. In a similar study using gastric carcinoma tumor samples, tumor-related gene methylation levels were measured to determine whether lifestyle factors prior to cancer diagnosis, including physical exercise, obtained through patient questionnaires, influenced methylation status. Interestingly, although not significant, increasing physical activity hours per week correlated with decreased methylation levels of CACNA2D3, a gene in which low expression due to hypermethylation correlates with poor prognosis [62].

In another study, salivary samples were collected pre- and post-12-week exercise intervention in healthy adults to determine DNA methylation status in cancer-related genes [63]. Forty-five CpG sites in over 20 genes associated with breast cancer development and progression were analyzed. Baseline methylation levels significantly correlated with reported pre-study physical activity levels. Further, an increase in physical activity correlated with a significant decrease in DNA methylation in post-exercise intervention samples. This study demonstrates that exercise over a relatively short period of time (12 weeks) can change DNA methylation levels using 45 novel CpG sites related to breast cancer [63]. A clear correlation between physical activity levels and methylation of genes important in breast cancer has been further supported by two independent studies which identified APC, L3MBTL1, and 42 other genes as differentially methylated in patients who perform different levels of physical activity [64, 65].

These studies uncover exercise as an epigenetic regulator, which could be one mechanism by which exercise prevents cancer development. Future studies are necessary to understand and identify epigenetic markers modulated by exercise. Epigenetic modifications, therefore, represent exciting potential biomarkers for exercise and a possible mechanistic link between exercise and cancer risk reduction.

Exercise and Histone Acetylation in Healthy Tissue and Cancer

Histone modifications are posttranslational modifications including methylation, acetylation, and more which impact gene expression by altering the histones, leading to changes in chromatin configuration [66]. Histone-modifying proteins are divided into three types: “writers,” which add posttranslational modifications; “erasers,” which remove posttranslational modifications; and “readers,” which recognize certain histone marks and contribute to the posttranslational modification of histones.

While studies are limited, exercise has been demonstrated to regulate gene expression via histone modifications. In a rat model, in which stress and behavioral depression were induced using a chronic restraint model, 1 hour per day of voluntary wheel running exercise reversed depressive behaviors caused by upregulation of oxytocin and arginine vasopressin expression in the brain [67]. In the study, the exercise intervention correlated with histone modifications. Specifically, after chronic restraint, H3K9 methyltransferases, which facilitate H3K9 methylation causing reduced gene transcription, were significantly reduced, resulting in decreased methylation at oxytocin and arginine vasopressin promoters and increased expression. When an exercise intervention was used in combination with the chronic stress model, H3K9 methyltransferase G9a was significantly increased, which restored H3K9 methylation and reduced oxytocin and arginine vasopressin, protecting against depressive behaviors [67]. Exercise also had a protective effect in an acute stress restraint animal model where decreases in global DNA methylation in areas of the brain were observed after stress; however, animals exposed to stress restraint with an exercise intervention had no change in global DNA methylation status [68].

Exercise also activates cellular stress pathways like AMP-activated protein kinase (AMPK), promoting various downstream signaling including the NAD-dependent histone and protein deacetylase, SIRT1 [69, 70]. Histone deacetylation is usually associated with tighter association of chromatin and histones, creating a "closed" formation, which is associated with reduced gene expression. Interestingly, in animal models, exercise was recently shown to increase SIRT1 protein in muscles, suggesting a role of exercise-induced histone modification through increased SIRT1 expression [71]. However, studies are needed to elucidate the epigenetic role of SIRT1 in response to exercise.

The impact of exercise on histone modifications specifically within tumors is understudied. However, there is evidence demonstrating a relationship between exercise and histone modifications in immune cell populations in cancer patients, revealing that exercise may induce epigenetic changes altering the tumor microenvironment. Intense endurance exercise consisting of running a half marathon increased histone acetylation and expression of NK functional marker, NKG2D, demonstrating that exercise activates NK cells in cancer patients and healthy individuals [72]. Interestingly, moderate 30-minute bicycle exercise increased $CD8^+$ T lymphocyte histone 4, lysine 5 (H4K5) acetylation in non-Hodgkin's patients and healthy controls; therefore, exercise also impacts T cell epigenetic regulation which may have implications in antitumor immune cell functioning in cancer patients [73]. Further studies are needed to confirm the full extent to which exercise influences histone modifications in cancer and the cancer microenvironment.

Although exercise has a robust effect on epigenetic regulation and links to cancer development and progression, it is important to note that several studies discussed reported non-significant trends which may be due to a small sample size or to a variation in the physiological response to exercise between individuals. In other studies, no epigenetic changes were observed after exercise intervention [74].

However, the large variation in study design, including tumor types and physical activities analyzed, likely accounts for the disagreement in results. Further research to elucidate the effects of exercise on DNA methylation and histone modification is essential to form a comprehensive understanding of exercise's implications in cancer development and prognosis.

MicroRNAs, Exercise, and Cancer

MicroRNAs (miRNAs) are a family of small noncoding RNAs that modulate gene expression [75]. There are over 2000 currently known miRNAs in the human genome which participate in vital processes including development, metabolism, signaling, and more [76]. In cancer, miRNAs that promote tumorigenesis are termed oncomiRs. OncomiRs promote cancer development and progression by reducing expression of tumor suppressors or increasing expression of oncogenes [77]. While a clear relationship between exercise and miRNA levels has been established and a relationship between miRNAs and cancer development is well described, data directly linking exercise-induced changes in miRNA levels to cancer development is sparse. This section will highlight known links between exercise and miRNAs and one published report linking these to tumor growth.

As discussed in previous sections, wide variability in the type and duration of exercise, as well as in the specific miRNAs studied, makes it difficult to draw broad conclusions about the relationship between exercise and miRNA or circulating miRNA expression [78, 79]. This section aims to give a sampling of studies in order to leave the reader with the understanding that exercise can impact cellular and circulating miRNA levels. However, the direction and magnitude of change are likely different based on which miRNA (just as expression of different genes would be) and what physical activity are being considered.

In healthy human subjects, changes in particular circulating miRNAs varied with different exercise interventions including a brief maximum exercise test, moderate-level 4 hour bicycle exercise, endurance exercise (running a marathon), or a single bout of resistance training [48]. With the goal of understanding endothelial cell or muscle damage in response to exercise, the authors chose to measure plasma levels of miR-126, a highly expressed endothelial cell miRNA, as a marker for endothelial cell damage and miR-133 as a marker for muscle damage. Interestingly, brief maximum exercise and 4 hour moderate bicycling increased miR-126 levels with no change in miR-133, while resistance training increased levels of miR-133 but did not change miR-126. Differently, running a marathon resulted in increased levels of both miR-126 and miR-133 [48]. These results clearly demonstrate the range of effects various types of exercise can have on circulating miRNA, likely due to the differing levels of muscle and respiratory involvement. In summary, authors suggest less strenuous or brief bouts of exercise which do not reach an individual's maximum threshold cause damage to mainly endothelium, therefore causing upregulation of miR-126, while resistance training targets muscle, resulting in upregulation

of miR-133. Intense endurance exercise, in contrast, was suggested to upregulate both miR-126 and miR-133 due to the overall strenuous nature and long bout of activity [48].

In another study, Nielsen et al. investigated the impact of a single acute bout versus a 12-week chronic exercise regimen on circulating miRNA plasma signatures [80]. Seven hundred forty-two circulating miRNAs were measured at 0 hours, 1 hour, and 3 hours after acute exercise. At 0 hours (immediately post-exercise), the eight miRNAs that significantly changed were downregulated, while 1 hour and 3 hours after acute exercise, all miRNAs that significantly changed (5 and 1 miRNAs, respectively) were upregulated. In contrast, after a chronic exercise regimen, seven miRNAs were significantly downregulated, and two miRNAs were significantly upregulated [80]. Interestingly, there were few overlapping circulating miRNAs altered by acute versus chronic exercise, demonstrating that acute and chronic exercise likely cause miRNA alterations through differing mechanisms. However, likewise a portion of circulating miRNAs that changed in response to both acute and chronic exercise was cardiac or skeletal muscle specific [80].

Changes in cellular miRNA levels in immune cell populations have also been demonstrated in response to exercise. In NK cells, isolated from blood of healthy men, before and after intense exercise, 23 miRNAs and 986 mRNAs were significantly changed. Interestingly, analysis identified pathways related to cancer signaling, adhesion molecules, and p53 signaling. Thus, exercise likely influences NK cell gene expression and miRNA levels, causing modulation of pathways known to regulate cancer development and progression [81]. A similar study identified 34 miRNAs that were significantly altered in PBMCs of healthy young men by an acute bout of intense exercise. Pathway analysis revealed that these miRNAs play roles in inflammation, demonstrating a novel concept of exercise-induced inflammation through miRNA regulation [82]. Neutrophils were also found to have changes in miRNAs associated with inflammatory pathways in response to exercise [83].

While exercise or physical activity clearly changes miRNA expression, which is likely to impact tumor growth, direct linkage of the two is currently unclear. Using mouse models, Isanejad et al. found in a breast cancer mouse model that interval exercise training alone and in combination with hormone therapy significantly reduced tumor volume [84]. Levels of angiogenic factors in the tumor tissue were also reduced in comparison to sedentary controls. Reduction in tumor growth and angiogenesis correlated with increased miR-206 and let-7a and decreased miR-21 in exercise and hormone-treated samples, demonstrating that exercise may influence tumor growth through miRNAs related to angiogenesis [84].

There are current reviews discussing exercise and miRNAs in cancer; however, they summarize miRNAs regulated by exercise and implicated in cancer progression [79, 85]. Interestingly, Dufrense et al. focuses on evidence reporting circulating levels of miR-133, miR-222, miR-221, miR-126, and let-7, all important miRNAs in various cancer types, to be altered in response to acute or physical exercise [79]. While enthusiasm for understanding the link between exercise, miRNAs, and cancer is present, as yet, an in-depth understanding of this link is lacking and not supported by data.

Other Emerging Mechanisms

Myokines

In recent decades, skeletal muscle has been recognized as an endocrine organ that secretes and responds to numerous growth factors, cytokines (known as myokines when secreted by contracting myocytes), hormones, and other signals. Some of the most well described include interleukins (IL-6, IL-8, IL-15), myostatin, irisin, secreted protein acidic and rich in cysteine (SPARC), and fibroblast growth factor (FGF) family members [41, 86]. In addition to being secreted by muscles in response to contraction, these factors have been implicated in tumor development, growth, or therapeutic response in various tumor models. Thus, muscle is highly likely to crosstalk with tumor cells and impact tumor development. Emerging evidence supports the likelihood of exercise impacting the crosstalk between muscles/myocytes and tumors/tumor cells [39, 87, 88] and has been well reviewed [86, 89].

Activation of p53 by Exercise

The master regulator of apoptosis, p53, is a critical tumor suppressor that is mutated or deleted in many cancer types. Appropriate activation of p53 in response to stress induces cell death and is therefore protective against cancer. Exercise induces p53 activation in muscle, and p53 is important for mitochondrial biogenesis and exercise capacity [90]. Thus, it is not surprising that p53 may play an important role in the protective effects of exercise against cancer. Exercise training of female rats during puberty correlated with significant upregulation of p53 mRNA, as well as BRCA1 and ERB mRNA, in mammary glands when rats reached 100 days old [91]. Similarly, voluntary wheel running caused significant upregulation of p53 in A549 lung carcinoma tumors in mice [92]. In addition to directly activating p53 in precancerous lesions, exercise appears to cause upregulation of systemic factors that cause p53 stabilization in LNCaP prostate cancer cells [93]. These studies demonstrate that exercise can impact p53 activation, at least within certain contexts. Given the critical role of p53 in numerous cancers, this potential mechanism is likely to become a major area of focus in the field.

Summary

In healthy humans and animals, physical activity or exercise causes changes to many systems of the body, including the cardiovascular, musculoskeletal, immune, and others. The molecular mechanisms by which these changes occur in the absence of disease are becoming clearly understood. In recent decades, the impact of these

exercise-induced changes on tumor development, progression, treatment, and survivorship has gained focus in the cancer biology and exercise physiology communities. As our mechanistic understanding of exactly what exercise does and how in the context of cancer grows, so will the ability to utilize exercise in a preventive or therapeutic setting.

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Part II
From Diagnosis Through Treatment

Chapter 5
Exercise Oncology from Diagnosis to Treatment: An Overview of Outcomes and Considerations

Ciaran M. Fairman and Daniel A. Galvão

Introduction

Advances in cancer therapies have been instrumental in improving survival rates in a variety of cancer types and stages. Unfortunately, it is well established that individuals who are exposed to different cancer therapies experience wide-ranging acute and persistent toxicities [1, 2]. Musculoskeletal impairments, cardiovascular dysfunction and body composition alterations are among the commonly reported side effects of various cancer treatments that are compounded by aging and inactivity [3–7]. These physiological impairments put individuals at a heightened risk of treatment-related toxicities, reduced physical function, cardiovascular disease, metabolic syndrome and cancer-related and all-cause mortality [8–12]. Although recent advances in screening, detection and treatments have resulted in an increase in the 5-year survival rate in a variety of cancers, the result is an increased proportion of individuals burdened by the physical and psychosocial consequences of treatment [13]. Fortunately, there is mounting evidence, built over the last three decades, indicating that exercise can protect against many of these treatment-related toxicities. The early work by Winnigham et al. in the 1980s [14–16] and Dimeo in the 1990s [17–19] and the influential first randomized controlled trials published in the *Journal of Clinical Oncology* in 2001 and 2003 by Segal [20, 21] and Courneya [22], which led to an accompanying editorial from the journal [23], provided a critical platform for the area we now know as *exercise oncology* to expand substantially.

In this chapter, we [1] provide a brief overview of common cancer treatments and adverse effects, [2] describe examples from early studies undertaken during treatment leading to the development of the PEACE framework, [3] present examples of contemporary trials in exercise oncology including those from pretreatment to

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during treatment phases, [4] discuss different study endpoints and outcomes from trials and how these have evolved and progressed over the past four decades and finally [5] provide considerations and future opportunities in this well-established and yet continuing area of research growth in exercise oncology.

Common Treatment and Adverse Effects

The magnitude of impairments in physiological systems or psychosocial wellbeing will vary based on the cancer site, treatment dose, duration, sequence or combination [24, 25]. An overview of common impairments from various cancer treatments is provided in Table 5.1. Surgery to remove the tumour and/or surrounding tissue is associated with local impairments in form and function of the tissue or organ. The extent of limitations experienced from surgery will vary based on the location and type of tumour. It's possible that surrounding tissues/organs may be affected. For example, removal of soft tissue sarcoma may involve the removal of surrounding muscle tissue, resulting in impairments in function [26, 27]. Lymphedema, defined as a protein-rich swelling of the body, particularly in the extremities, is another concern especially in breast cancer [28].

Radiotherapy is used to damage genetic material of DNA, limiting the ability of cancer cells to divide and proliferate. Radiotherapy typically damages the tissue that is being irradiated, though surrounding organs and tissue may be affected as well. Fibrosis to cardiac or lung tissue can have long-term effects on cardiopulmonary function [29, 30].

Whilst surgery and radiation are typically used to treat cancer locally, chemotherapy acts systemically, working throughout the whole body to target and kill rapidly dividing cells. Due to the systemic nature of this treatment, it can impact healthy cells and has a variety of acute and persistent toxicities that vary according to the specific agent used, mechanism of action, dose and duration of administration. Nausea, fatigue, weakness and gastrointestinal distress are particularly evident during active therapy [31–34]. Importantly, chemotherapy is associated with many serious persistent side effects. Cognitive function and memory can be affected for many years following the cessation of treatment [35]. Cardiotoxicity is of chief concern, particularly in individuals receiving anthracycline chemotherapy [3, 9, 36, 37]. Chemotherapy-induced peripheral neuropathy (CIPN), resulting in numbness in the hands and feet along with balance impairments, is particularly evident with taxane-based chemotherapeutic agents, with evidence of symptoms of CIPN up to several years after treatment [38]. Weight changes are also common, though the direction and magnitude of change can differ based on the type of cancer, chemotherapeutic agent, administration of corticosteroids and concomitant therapy along with lifestyle factors [39, 40].

Hormone therapy is most commonly used in the treatment of breast and prostate cancer, using exogenous hormones or surgery to either block hormone receptors or interfere with hormone production. The magnitude of side effects experienced is

Table. 5.1 Overview of common impairments from various cancer treatments

	Fatigue	Pain	Cardiovascular dysfunction	Pulmonary changes	Peripheral neuropathy	Cognitive changes	Body composition changes	Bone Health	Immune system change	Lymphedema	Gastrointestinal Distress
Surgery	•	•		•		•	•			•	•
Radiotherapy	•	•	•	•		•	•		•	•	•
Chemotherapy	•	•	•	•	•	•	•	•	•		•
Hormonal therapy	•	•	•			•	•	•	•		•
Targeted therapies	•	•	•			•			•		•

Adapted from Schmitz et al. [112]

based on a variety of factors, including the type of therapy received, mechanism of action and treatment duration. Hormone therapy for breast cancer is associated with postmenopausal symptoms such as hot flashes, joint pain, fatigue, weight gain and dyslipidaemia [41, 42]. Androgen deprivation therapy for prostate cancer is consistently associated with a reduction in muscle mass and bone mineral density. This, coupled with a pronounced accumulation of body fat, dramatically increases the risk of further cardiometabolic damage and disease risk (i.e. obesity, hypertension, insulin resistance, dyslipidaemia) [43]. Additionally, it has been proposed that physiological and psychological impairments as a result of cancer treatment can accelerate functional decline and the trajectory towards a disability condition [1, 2].

Targeted therapies aim to stop the growth and spread of cancer by interfering with specific molecules, such as genes, proteins or the tissue environment contributing to cancer growth. Immunotherapy attempts to use elements of the immune system mostly to combat cancer. Due to the specific or "targeted" nature of these treatments, healthy cells are not as readily affected as other treatments, though most commonly reported side effects include dermatological, such as damages to the skin, hair and nails [44, 45]. Additionally, fatigue and muscle aches are also commonly reported side effects of targeted therapies and immunotherapy [46]. Clearly, the deleterious, often long-lasting effects of various cancer therapies identify a critical area of concern. Mounting evidence indicates that exercise may be useful in managing many of the side effects of common cancer therapies. The subsequent sections of this chapter will be focused on providing an overview of the extant literature on the role of exercise in the prevention and management of cancer treatment side effects from diagnosis through the end of treatment. A hypothetical trajectory of physiological systems affected by various cancer treatments with no exercise and various opportunities for exercise participation along the cancer continuum to mitigate cancer-related adverse effects and preserve/enhance physiological capacity is presented in Fig. 5.1.

From Early Studies to the PEACE Framework

In this section a brief perspective of the exercise oncology research is presented with the earliest research published in the mid-1980s. Cunningham et al. examined the effects of a resistance exercise in patients with acute leukaemia [47]. Participants were randomized to either 3 or 5 days per week of exercise or a non-exercising group for 5 weeks. Outcomes of interest were nitrogen balance, creatinine excretion, skinfold measures and arm circumference. There were no changes in anthropometric measures or nitrogen balance over the course of the intervention. However, the authors suggested that decreasing levels of creatinine excretion from pretest to posttest indicated a favourable response in both training groups. Winnigham et al. investigated a 10-week aerobic exercise program in breast cancer patients undergoing chemotherapy [15]. Participants were randomized to supervised aerobic exercise 3 days per week, a flexibility program 1 day per week or a non-exercising control.

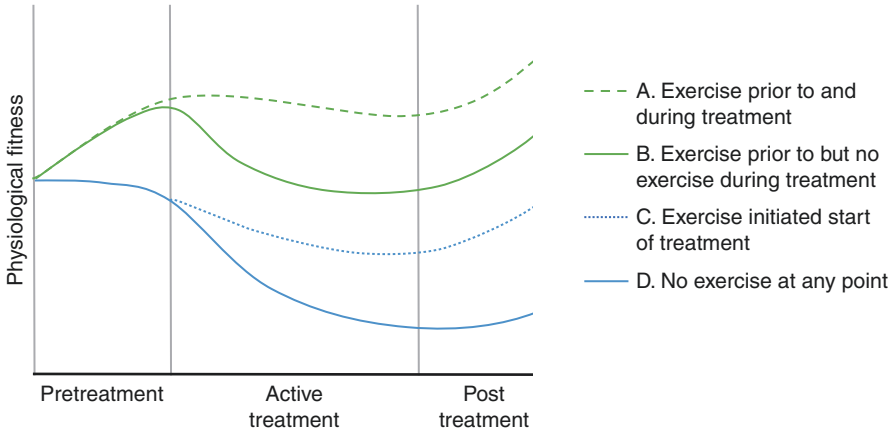

Fig. 5.1 Hypothetical trajectory of physiological systems in accordance with exercise participation along the cancer continuum. (**a**) Theoretical trajectory of physiological fitness of those who begin exercise at diagnosis and through treatment. It is hypothesized that prehabilitation and continued exercise during treatment would yield the most favourable results in buffering the side effects of treatment, providing the greatest likelihood of resuming normal activity and fitness levels after treatment. (**b**) Prehabilitation alone without exercise during treatment could result in some improvements in physiological fitness that would most likely be lost during treatment without activity, as documented by reports of the magnitude of treatment toxicities experienced by inactive individuals receiving treatment. (**c**) Individuals who do not participate in exercise prior to treatment but begin at the onset of treatment would likely experience a "buffering" effect of exercise, whereby reductions of physiological fitness are lessened or reversed compared to those who do not participate in exercise. (**d**) Those who are inactive throughout the entire treatment continuum are likely to experience the greatest reductions in physiological fitness, in addition to a blunted recovery of these systems following the cessation of treatment

The primary outcome of nausea was significantly improved in the exercise group compared to the flexibility and control groups. This early work was critical in highlighting the preliminary safety of participating in exercise during cancer treatment.

Dimeo et al. [18] followed this early work by expanding on the investigation of exercise during high-dose chemotherapy before autologous blood stem cell transplantation. The authors demonstrated that compared to non-exercising controls, hospital-based aerobic exercise was associated with attenuation of physical decline and a reduction in duration of thrombopenia and neutropenia and length of hospital stay [18]. An important landmark in the field of exercise oncology occurred with the publication of the results of a trial in the *Journal of Clinical Oncology* in 2001 by Segal et al. [20]. This trial investigated the effects of self-directed or supervised exercise in breast cancer patients receiving treatment (chemotherapy, hormonal therapy or radiotherapy) [20]. Results of the trial revealed that exercise was associated with improvements in physical function and a reduction in body weight. This publication in a prestigious cancer journal provided the field of exercise oncology with great exposure to the medical community and served to bolster the credibility of the line of research.

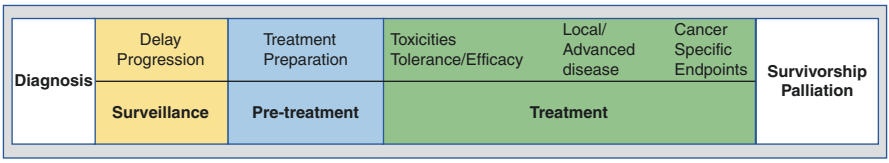

Fig. 5.2 Adapted PEACE framework to include surveillance, pretreatment and treatment

The first 10–15 years of research in the field of exercise oncology was critical in providing evidence contrary to the prevailing dogma that bedrest would be most beneficial for individuals receiving cancer treatment. The culmination of this work resulted in the PEACE framework, proposed by Courneya in 2001 [48]. This framework, which was modified in 2007 [49], has served as the reference point of exercise oncology research for almost two decades. The updated framework splits the cancer experience into six time points, two pre-diagnosis (prescreening and screening/diagnosis) and four post-diagnosis (pretreatment, treatment, survivorship and end of life). Accompanying the six time points are eight cancer control outcomes that are proposed to be responsive to physical activity interventions. These are prevention and detection during the pre-diagnosis phase and treatment preparation/coping, treatment effectiveness/coping, recovery/rehabilitation, disease prevention/health promotion, palliation and survival in the post-diagnosis phase. For the purpose of this chapter, we have adapted the PEACE framework (Fig. 5.2) to include [1] surveillance/pretreatment and [2] treatment phases with the latter divided into (I) treatment-related toxicities, (II) treatment tolerance/efficacy, (III) treatment in patients with advanced disease and (IV) cancer-specific endpoints.

Diagnosis

A diagnosis of cancer is often seen as a "teachable moment", where individuals may be more amenable to adopting healthy lifestyle behaviours [50]. Research has demonstrated that individuals with a diagnosis of cancer may be more receptive to information about the role of healthful lifestyle behaviours (i.e. dietary modifications, physical activity, smoking cessation, etc.) with the potential to increase the adoption and maintenance of these behaviours [51]. Broadly speaking, it is recognized that this is a key time to introduce interventions aimed at modifiable risk factors that may increase the likelihood of the successful adoption and maintenance of these behaviours. Importantly, this teachable moment and the discussions of lifestyle behaviours have to be balanced with the broader patient experience and the impact of receiving a cancer diagnosis, making important decisions on course of treatment, financial obligations and work/family commitments. Thus, on an individual level, the "art" of exercise oncology is making an informed decision on how and when to introduce the topic of lifestyle behaviours.

Surveillance and Pretreatment

Clinical interest of exercise has emerged for patients who are managed with surveillance due to low volume, stage and grade of some cancers [52]. For example, active surveillance for prostate cancer describes a management strategy that involves no active treatment with regular monitoring with an intention to proceed to treatment with a curative intent when evidence of a clinically relevant change from a low-risk cancer becomes evident [53]. Preliminary evidence suggests that lifestyle and/or exercise interventions might have therapeutic potential for men on active surveillance [52]. In an early study in which patients made lifestyle changes during 1 year involving use of stress management techniques, dietary changes and physical activity (walking for 30 min, 6 days per week), a significant reduction of 4% in serum prostate-specific antigen (PSA) levels was observed in the intervention, whilst a 6% increase occurred in the non-intervention group [54]. After a follow-up period of 2 years, 27% of patients in the non-intervention group and 5% of patients in the intervention group had undergone conventional treatments (radical prostatectomy, radiotherapy and/or ADT) with a curative intent [55]. A recent study examining feasibility, safety and acceptability of aerobic exercise in the setting of active surveillance in 50 men with prostate cancer over 12 months reported improvements in body mass, systolic and diastolic blood pressure and quality of life [56]. Current exercise studies and efforts to expand these important initial findings are examining the potential of long-term exercise interventions implemented during surveillance to delay cancer progression and transition to active therapies [57].

The treatment preparation phase centres around the premise of "prehabilitation" and aiming to minimize the burden and impairments experienced from cancer treatments. First-line treatment for cancer is usually surgery to resect the tumour and surrounding tissue. Resultantly, impairments in the form and function of tissues and organs are a primary concern. Further, low muscle mass at diagnosis is consistently associated with greater treatment-related toxicities and overall mortality in a variety of cancers. Consistent evidence indicates that individuals diagnosed with cancer reduce levels of physical activity from pre- to post-diagnosis [58, 59]. This reduction in activity and subsequent "detraining" is likely to contribute to treatment-related toxicities, worsening of body composition and poorer prognosis. This highlights the urgent need to investigate interventions that can result in positive physiological adaptations in the pretreatment period that will potentially allow for greater treatment tolerance, reducing the magnitude of impairments resulting from therapy.

Interestingly, though the clinical utility of prehabilitative training is well supported, this remains one of the most difficult phases to study for a variety of issues. Primarily, the pretreatment period has varying durations, some lasting days or weeks, others lasting months. This makes the design and practical implementation of exercise interventions challenging. Additionally, the time surrounding a diagnosis brings a host of changes for patients, including psychological stress, financial burden and time management issues, all of which can affect an individual's proclivity to participate in an exercise program during this period. Consequently, this

remains an understudied area of research in exercise oncology. In an early single-arm pilot study, Jones et al. [60] reported that pre-surgical exercise training improved exercise capacity in lung cancer survivors undergoing pulmonary resection.

Licker et al. [61] examined the effects of high-intensity interval training (HIIT) prior to lung cancer surgery. Individuals with operable lung cancer were randomized to an HIIT group or no exercise control. The exercise group underwent ~25 days of HIIT (two 10-minute series of 15-second sprint intervals (at 80–100% peak work rate) separated by 15-second pauses and a 4-minute rest between the two series) prior to surgery. The primary outcome measure was a composite of death and in-hospital post-surgery complications. The 6-minute walk test, peak heart rate and peak oxygen consumption were also obtained. The results indicated that whilst exercise resulted in significant improvements in aerobic performance, there were no differences in early complications following surgery [61].

A review by Singh et al. [62] examined pre-surgical interventions and their effects on clinically relevant outcomes in cancer patients. The review included a mix of studies in lung, prostate and colorectal cancer patients. Overall, the results supported pre-surgical exercise through aerobic and resistance training, either on their own or in combination, to be beneficial in improving aerobic fitness, QOL and physical function. Importantly, the majority of studies included in the review were in lung cancer patients before a lung resection, so the evidence of the efficacy of prehabilitation is somewhat limited to this population. Additionally, very few studies included a control group or have carried out interventions to detect differences in outcomes between exercise interventions performed prior to, during or after treatment.

A recent study addressing some of the limitations reported above was conducted by Santa Mina et al. [63] where 87 prostate cancer patients were randomized to either receive a home-based exercise prehabilitation plus pelvic floor training or control condition of pelvic floor training alone prior to undergoing radical prostatectomy. Results indicated improved functional capacity and reduced preoperative and 6-month post-operative anxiety. Although not a primary study endpoint, post-operative complications as well as hospital length of stay was similar between groups at follow-up assessments.

Clearly, more research is required to expand on current findings in this phase of pretreatment. However, this is one of the most challenging areas of exercise oncology research as patients are typically trying to process and cope with a cancer diagnosis and get their affairs in order as they prepare for treatment. This, coupled with a relatively short time period between diagnosis and treatment, makes this a difficult window to recruit participants to conduct research.

During Treatment: Prevention/Reduction of Treatment-Related Toxicities

The investigation of exercise interventions during active cancer treatment is one of the fastest growing areas of exercise oncology. Ultimately, the goal of exercise during treatment is to manage treatment side effects, attenuate physical decline,

facilitate the completion of treatment and potentially enhance treatment efficacy. The effects of exercise during treatment have been summarized by numerous systematic reviews and meta-analyses, all with the general consensus that exercise can at minimum attenuate, if not improve, some of the treatment-related decline in skeletal muscle mass, muscular strength, cardiovascular function, fatigue and certain dimensions of quality of life [64–67].

Cardiac dysfunction is of critical concern in cancer treatment, particularly anthracycline chemotherapy agents, mediastinal irradiation and molecular targeted therapies [3, 9, 36, 37]. The magnitude of cardiac dysfunction is associated with the individual and cumulative dose and combination and/or sequence of drugs administered. Resultant cardiac arrhythmias, left ventricular dysfunction, myocardial ischemia, fibrosis and arterial thrombosis can lead to an increased risk for cardiovascular disease and related mortality in individuals with cancer [36, 68, 69]. Clearly, the prevention and/or attenuation of cardiac dysfunction from cancer therapies is of critical concern.

The evidence supporting the efficacy of exercise to mitigate the cardiotoxic effects of cancer treatment remains limited. Nevertheless, several randomized controlled trials show promise. Segal et al. compared the effects of resistance training or aerobic training versus usual care in individuals with prostate cancer initiating radiotherapy. Results demonstrated that both exercise groups attenuated a 5% decline in VO_2 peak observed in the usual care group [70].

Results from a trial by Courneya et al. evaluating an aerobic exercise program in individuals with Hodgkin or non-Hodgkin lymphoma during chemotherapy demonstrated that mean VO_2 peak increased by 4.6 ml/kg/min in the exercise group compared with a decrease of 0.6 ml/kg/min in the control group [71]. In a recent meta-analysis of clinical trials investigating the effects of exercise on cardiovascular outcomes in patients with cancer, Scott et al. demonstrated that exercise was associated with a significant increase in VO_2 peak (+2.80 ml/kg.min) compared with no change (+0.02 m/kg/min) in controls. However, the analysis included exercise interventions that were implemented before, during and after cancer treatment [72]. Currently, the extent by which exercise can attenuate cancer treatment-related cardiac dysfunction during cancer treatment is unclear [37]. Further, VO_2 peak may also be influenced by factors other than cardiac impairments, such as bone marrow suppression (and subsequent red blood cell production), muscular impairments and blood volume regulation in cancer patients, making it difficult to use VO_2 peak as an accurate indicator of cardiotoxicity [73]. Future work may be needed to investigate the type, dose and timing and mechanisms by which exercise may offer cardioprotection in individuals with cancer.

Individuals with cancer are exposed to a variety of factors that result in loss of muscle mass, including cancer therapies, tumour burden and malnutrition that are compounded by aging and inactivity. The importance of the maintenance of muscle mass during treatment cannot be overstated, with consistent evidence demonstrating the association between low muscle mass and treatment-related toxicities, cancer and all-cause mortality.

Galvão et al. [74] reported the results of a 12-week combined resistance and aerobic training intervention in men with prostate cancer receiving androgen

deprivation therapy with some undergoing concurrent radiation. Participants were randomly assigned to either an exercise (n = 29) or non-exercise control group (n = 28). The adjusted mean difference after the intervention for total body and regional lean mass was approximately 1 kg favouring the exercise group. Loss of lean mass after initiation of androgen deprivation has been extensively documented [7, 75], indicating the importance of targeted exercise to preserve musculoskeletal health in this group of patients.

Courneya et al. conducted a randomized controlled trial of aerobic exercise, resistance exercise or usual care (outlined in greater detail later) in individuals with breast cancer beginning adjuvant chemotherapy. Results of the trial revealed the resistance exercise group experienced a 1 kg increase in total body lean mass compared to the aerobic group (0.5 kg) and control group (−0.2 kg). Though promising, these results are in contrast to other trials that demonstrated no effect of exercise on muscle mass. Demark-Wahnefried et al. [76] found no effects of exercise on muscle mass in a combined home-based aerobic and resistance exercise intervention in individuals undergoing chemotherapy/radiotherapy and hormone therapy. Mustian et al. [77] found no effects of a combined home-based aerobic and resistance exercise intervention on muscle mass in breast and prostate cancer patients receiving radiotherapy. Taken together, these results indicate that supervised interventions may be superior to home-based intervention at targeting muscle mass in individuals with cancer.

Considering the association of low muscle mass with increased treatment toxicities, poorer prognosis and cancer-related and all-cause mortality, strategies to improve muscle mass are of clear clinical importance. However the extant literature remains mixed, with insufficient evidence to draw firm conclusions on the effect of exercise on muscle mass in individuals with cancer undergoing treatment [78]. The heterogeneity of results is likely linked to a variety of factors including quality and length of the exercise interventions, level of supervision provided, course of cancer treatment and prior activity levels. It should be noted however that, given the documented reductions in muscle mass with aging and various cancer treatments, the preservation of muscle mass (particularly when coupled with improvements in muscle strength) should also be seen as positive.

Fatigue is a ubiquitous, distressing symptom of cancer treatment, with approximately 50–90% of individuals receiving treatment experiencing fatigue [79]. Importantly, cancer-related fatigue is distinguishable from “regular” fatigue in that it is a complex, multifactorial syndrome, not fully ameliorated by rest. Several contributing factors have been proposed, including systemic inflammation, dysregulation of the hypothalamus-pituitary-adrenal axis, depression, anaemia and physical inactivity. There is consistent evidence to suggest that exercise is effective at ameliorating cancer-related fatigue. Peutz and Herring conducted a meta-analysis of exercise interventions on cancer-related fatigue during and after cancer treatment [80]. The results revealed similar magnitude effects both during and after treatment, with the greatest improvements in fatigue experienced by those with the lowest baseline scores and higher intervention adherence [80]. The results of a recent meta-analysis demonstrated that there is insufficient evidence to indicate if a

modality or specific prescription of exercise may be the most effective to target cancer-related fatigue [81]. A positive consequence of this is that most exercise modalities appear to have similar impact on fatigue with moderate-to-large effect sizes [81]. Similarly, Taaffe et al. recently reported in a large yearlong randomized controlled trial with 163 prostate cancer patients that different exercise modes had comparable effects on reducing fatigue during treatment [82]. Moreover, it appears that the greatest effects of exercise on fatigue are in those with greatest levels of fatigue at baseline [80, 82, 83]. Consequently, practitioners can make an informed choice of exercise selection based on availability of equipment, time, location and patient preferences.

Individuals receiving cancer treatment (i.e. hormonal therapy, chemotherapy and glucocorticoids) are at a heightened risk of bone loss. Recent evidence indicates that bone mineral density (BMD) loss associated with different cancer therapies can range between 2.0% and ~8% at 1 year [84]. This rate of bone loss is particularly concerning when compared to a rate of ~1% per year in apparently healthy individuals [84]. The accelerated decline in bone health can place individuals receiving cancer treatments at a heightened risk of fractures. Consequently, the importance of maintaining bone health during cancer treatment is critical.

It is being increasingly well recognized that bone may respond more favourably to high-impact exercises, highlighting the need of interventions to target specific outcomes of interest. In a yearlong trial, Newton et al. recently investigated the comparative efficacy of impact loading + resistance training, aerobic + resistance training and delayed aerobic exercise on bone mineral density in 154 prostate cancer patients undergoing androgen deprivation therapy [85]. Results of the trial revealed that impact + resistance exercise attenuated a decline in spine and hip BMD compared to aerobic + resistance exercise and delayed aerobic exercise. These findings are of clinical importance given that exercise is likely to be lower in cost than commonly used pharmacological therapies for bone loss (bisphosphonates) which also have low compliance [86].

An important concern among individuals who receive a cancer diagnosis is the psychological impact of the diagnosis and multifaceted burden of ensuing treatments. Consequently, individuals with cancer regularly experience anxiety, sleep disturbance and stress that is associated with decrements in aspects of health-related quality of life (HRQOL) and depression. In a recent meta-analysis of exercise interventions either during or at the initiation of treatment for cancer, Mishra et al. found that exercise interventions had a positive impact on overall health-related quality of life (HRQOL) and certain subdomains including physical functioning, role functioning and social functioning [87]. Moreover, improvements may be greater when prescribed at moderate-vigorous intensity versus lower intensity. This supports other works indicating the exercise may result in positive improvements in stress, anxiety and symptoms of depression [88, 89]. Collectively, there is a burgeoning body of evidence supporting the role of exercise offering some sort of psychosocial relief during cancer treatment. Further research is warranted to determine the sustainability of these effects after cancer treatment.

Exercise Timing: How Soon Should We Intervene?

There is an increasing interest among clinicians and researchers as to when would be the most opportune time to intervene with exercise. As such, questions of timing of exercise implementation for cancer patients remain an understudied area. In a recent trial of 104 prostate cancer patients, Taaffe et al. investigated the effects of an immediate versus delayed exercise intervention in men initiating androgen deprivation therapy [90]. Participants randomized to the immediate exercise group participated in 6 months of supervised aerobic, resistance and impact exercises, three times weekly. Participants in the delayed exercise group who underwent usual care for 6 months followed the same 6-month program as the immediate exercise group. Lumbar spine was preserved in the immediate exercise group compared to the delayed group (0.4% vs. −1.6%, respectively) at 6 months. Additionally, lean mass, appendicular skeletal mass and muscle density were preserved in the immediate exercise group and recovered at 12 months in the delayed exercise group. Results of this study indicate that initiating exercise at the onset of androgen deprivation therapy may be an important strategy to prevent or attenuate treatment-related musculoskeletal toxicities in prostate cancer patients.

Decisions on the appropriate timing of the intervention may be related to the cancer site or treatment course/burden. Capozzi et al. investigated the effect of a 12-week lifestyle and resistance exercise intervention either during radiation treatment or delayed until after treatment in individuals with head and neck cancer [91]. The primary outcome of body composition (more specifically, lean body mass) was assessed at 12 and 24 weeks. Both groups experienced similar reductions in body mass (exercise during radiation, −8.1 kg; exercise after radiation, −8.8 kg) and lean body mass (exercise during radiation, −4.9 kg; exercise after radiation, −5.4 kg) during treatment, which remained at 24 weeks. Interestingly, exercise attendance was 45% for the intervention during treatment for the exercise group during radiation and 61% for the intervention following treatment for the exercise group after radiation. The authors concluded that the implementation of an exercise program for individuals initiating treatment for cancer treatment may not be feasible for some individuals due to the stressful physical and psychological demands of head and neck cancer treatment.

These studies highlight some of the challenges of determining the most opportune time for exercise interventions in individuals diagnosed with cancer. Currently, there is a paucity of research investigating the timing of exercise interventions across the cancer continuum to optimize adherence to exercise and improvement in clinically relevant outcomes. Clearly, the anticipated benefits of exercise in ameliorating treatment-related toxicities must be balanced with the broader view of the treatment schedule and physical and psychological burden on the patient that may offer unique barriers to exercise distinct from other time points along the cancer continuum. Theoretically, exercise should be commenced as soon as possible to buffer treatment-related toxicities and preserve the function of physiological systems. However, it's likely that this recommendation is going to be site specific along with considerations for treatment and anticipated barriers contrasted against anticipated benefits.

Whilst mounting evidence demonstrates that exercise can attenuate many treatment-related toxicities, there are numerous tumour sites that remain understudied. Additionally, research investigating the effects of exercise on treatment toxicity should look to delineate between prevention and treatment, in addition to designing the intervention to target the specific outcome of interest. Importantly, maintenance of the patient's current condition may also be deemed as the best possible outcome, particularly given the magnitude of toxicity for each treatment.

During Treatment: Tolerance/Efficacy

Courneya et al. conducted a randomized controlled trial to examine the effects of different exercise modalities in breast cancer patients receiving chemotherapy [92]. Participants (n = 242) were randomized to an aerobic exercise, resistance exercise or usual care group for the duration of chemotherapy (median, 17 weeks; 95% CI, 9–24 weeks). The primary outcome was cancer-specific quality of life. Secondary outcomes included fatigue, physical fitness, body composition, chemotherapy completion rate, lymphedema and psychosocial functioning. Results of the study indicated that neither aerobic nor resistance exercise improved cancer-specific quality of life. Physical fitness, body composition and self-esteem were improved in the exercise groups. Interestingly, the chemotherapy completion rate was 89.9% in the resistance exercise group, 87.4% in the aerobic exercise group and 84.1% in the usual care group. The reasons for the improved completion rate are unclear, though the authors did allude to the association between a completion rate of ~85% and clinical outcomes.

Van Waart et al. compared the effectiveness of a home-based exercise program versus supervised exercise or usual care in patients with breast cancer undergoing chemotherapy [93]. Primary outcomes were cardiorespiratory fitness, muscle strength and fatigue. Secondary outcomes include physical activity, psychological distress and chemotherapy completion rates. Participants in the home-based group participated in at least 30 minutes of low-intensity activity, 5 days per week. Individuals in the supervised program participated in a combined aerobic and resistance exercise two times per week. Both exercise groups began after the first cycle of chemotherapy and lasted until 3 weeks after the last cycle. Results of the trial indicated that both exercise groups had less decline in cardiorespiratory fitness and physical functioning than the usual care group. Additionally, both exercise groups experienced less pain, nausea and vomiting than the usual care group. Interestingly, significantly less patients in the supervised exercise group required dose adjustments to chemotherapy (12%) than the home-based (34%) or usual care groups (34%). Further, the average percentage dose reduction was 10% in both exercise groups compared to 25% in the usual care group. In a randomized controlled trial of 12 weeks of supervised aerobic training or usual care, Courneya et al. [71] demonstrated that supervised exercise did not interfere nor did it enhance treatment

completion or response in lymphoma patients undergoing chemotherapy. Taken collectively, these preliminary findings allude to a potential protective effect of exercise against treatment-related toxicities. Ultimately, higher chemotherapy completion rates are associated with an improvement in disease-free and overall survival.

Bland et al. recently conducted a systematic review, synthesizing the literature examining the effects of exercise on chemotherapy completion rates [94]. Eight randomized controlled trials were included in the final analysis. Of those, only two studies demonstrated a favourable effect of exercise on completion rate, with the remaining six trials demonstrating no difference with exercise and control. Taken collectively, there is insufficient evidence to conclusively report whether exercise has a beneficial effect on the delivery of chemotherapy. Future studies are warranted to examine the effects of exercise on chemotherapy completion rates and the association of these changes with cancer endpoints. More specifics on this evolving area of exercise and treatment tolerance/efficacy will be discussed in further detail in subsequent chapters.

During Treatment: Patients with Advanced Disease and Palliation

Palliation is a cancer control outcome if treatment is either contraindicated or unsuccessful. The purpose of palliation is to relieve symptoms and to reduce/delay the decline in function and quality of life at the end of life. Research in this area is still very limited, although preliminary evidence shows promise. Oldervoll et al. [95] examined the effects of a combined aerobic and resistance exercise program in 231 advanced cancer patients. Individuals were undergoing chemotherapy ($n = 65$, 53.7%), radiotherapy ($n = 9$, 7.4%), hormonal therapy ($n = 21$, 17.4%) or targeted therapy ($n = 5$, 4.1%). Participants in the exercise group experienced significant improvements in the shuttle walk test and handgrip strength, with no improvement in fatigue [95]. It should be noted that of the participants that agreed to take part in the study, 54% completed the intervention, with an average attendance of 69%. This suggests some potential challenges in delivering interventions in the advanced-disease population.

Jensen et al. examined the feasibility of an exercise intervention in a large sample of 500 terminal cancer patients receiving treatment [96]. The authors found that the intervention was well tolerated by the patients, but similar to Oldervoll et al., there was some loss to follow-up through patient mortality. Research in the palliation phase of the cancer continuum is extremely difficult and it remains a relatively understudied area. There is clear potential for the use of exercise interventions in palliative care to target physiological and psychosocial wellbeing, though there is a paucity of conclusive evidence in this area.

Galvão et al. [97] examined the efficacy and safety of a modular multimodal exercise program in prostate cancer patients with advanced disease and bone metastases. The exercise program comprised of resistance, aerobic and flexibility training

taking into consideration the location and extent of bone metastases as a strategy to maintain or enhance physical function in this group of patients with advanced disease. As a result, the program was based on a mechanical perspective to avoid direct loading to the metastatic lesions. Patients in this study had extensive bone disease with metastatic lesions present in the pelvis (75.4%), femur (40.4%), rib/thoracic spine (66.7%), lumbar spine (43.9%), humerus (24.6%) and other sites (70.2%) and were either receiving or treated with ADT/chemotherapy. After 12 weeks of exercise training, patients in the exercise group reported improved self-reported physical functioning. No skeletal fractures or increased bone pain was reported as a result of the intervention. Given that metastases to bone occur in approximately 80% of men with advanced prostate cancer [98] leading to significant morbidity, limited function and decreased quality of life [99–101], these initial findings suggested potential clinically meaningful benefits of exercise to patients with advanced disease and bone metastases.

During Treatment: Cancer-Specific Endpoints

As presented in previous chapters, consistent evidence from epidemiological studies have shown that higher levels of physical activity post-cancer diagnosis are associated with increased cancer-specific and overall survival [102, 103]. These studies introduced an important concept that beneficial effects of physical activity/exercise after a cancer diagnosis could in fact extend beyond improving symptoms and treatment toxicities as initially suggested. Based on this foundation, larger trials were initiated in recent years to investigate if exercise during treatment in fact may improve survival and other disease-related cancer-specific endpoints in patients with colon cancer that have recently completed adjuvant treatment, patients with haematological cancers receiving allogenic stem cell transplantation, patients with metastatic castrate-resistance prostate cancer (mCRPC) receiving a variety of treatment modalities (AR-targeted therapy, ADT, chemotherapy) and patients with ovarian cancer receiving first-line chemotherapy.

Although not during treatment, the Colon Health and Life-Long Exercise Change (CHALLENGE) trial was the first trial designed to examine the effects of a structured physical activity intervention on disease-free survival in stage II or III colon cancer patients who have completed adjuvant therapy [104]. The study is ongoing, and preliminary feasibility results of 273 participants across 42 international centres have been initially reported [105].

The Physical Exercise Training versus Relaxation in Allogenic stem cell transplantation (PETRA) Study is a randomized controlled trial investigating the effects of partially supervised aerobic and resistance exercise in patients during and after allogenic stem cell transplantation [106]. Two-hundred and fifty-six patients have been randomized into an exercise or muscle relaxation training program for 1 year in a combination of supervised and self-directed exercise. The exercise program consists of 3 sets of 12 repetitions with 6–10 exercises for major upper and lower

body groups 2–3 times per week. Endurance training will be prescribed three times a week in the form of walking or jogging, with intensity monitored using the RPE scale. Participants in the relaxation group will receive a manual with background information and an audio CD on muscle relaxation, along with a standard physiotherapy program and access to a treadmill, during the inpatient period. The primary outcome is overall survival after 2 years.

Global Action Plan 4 Intense Exercise for Survival Among Men with Metastatic Castrate-Resistant Prostate Cancer (Interval-GAP4) is designed to examine the effects of high-intensity aerobic and resistance training on overall survival in men with mCRPC [107]. Secondary endpoints include time to disease progression, biomarkers of inflammation, energy metabolism, androgen metabolism and quality of life. Eight hundred and sixty-six participants will be randomized to either supervised exercise or self-directed exercise for 2 years. Individuals randomized to supervised exercise will participate in an individualized, periodized exercise program. The resistance exercise will be modified in accordance with sites of bone metastases using a protocol previously demonstrated to be safe in this population. The aerobic exercise will be a combination of high-intensity interval training and moderate-intensity continuous exercise.

Lastly, the ECHO trial [108] is evaluating the effects of an exercise intervention during first-line chemotherapy for ovarian cancer on progression-free survival. The exercise program is being undertaken during the period of chemotherapy with follow-up assessments at 6 and 12 months. These studies add substantially to the pioneering CHALLENGE trial [104] by providing evidence on the casual effects of exercise on survival in patients with cancer.

The protective effects of physical activity on cancer recurrence and disease-free survival most likely lie in improved metabolic function, attenuation of the accumulation of body fat along the maintenance of independent physical function. These trials are the biggest of their kind in cancer and have the potential to dramatically impact the field of exercise oncology. The results from these trials will provide critical insight into the causal effects of exercise interventions on cancer survival. If successful, they will be paramount in providing evidence supporting the uptake of exercise in cancer survival. Moreover, the cost analysis from these trials will provide valuable information that encourages policy reform and third-party coverage of these services.

Outcomes and Considerations for Future Inquiry in Exercise Oncology from Diagnosis Through Treatment

As outlined in the beginning of this chapter, the adapted PEACE framework highlights some key areas of focus for research in cancer, from exercise through the end of treatment. Specifically, the pretreatment phase is centred around delaying the progression of disease and buffering the anticipated physiological/psychological impairments associated with various treatments. Importantly, future research in the pretreatment phase should look to explore how improvements in fitness are

associated with post-treatment complications and/or length of hospital stays following surgical procedures. This may provide important information that supports third-party reimbursement for these services in the future.

Overall, the extant literature demonstrates that exercise is safe and feasible in a variety of cancer types, undergoing different cancer treatments. Future research may look to investigate the effects and mechanisms of exercise on mitigation of treatment-related toxicities. Specifically, research should seek to differentiate between *prevention* of toxicities and *improvement* of symptoms. For example, investigating the effects of exercise on cancer-related fatigue should consider enrolling individuals with documented cancer-related fatigue to potentially enhance the response to the exercise intervention. Further, the exercise dose-response in intervention studies has been rarely investigated in relation to a variety of outcomes and endpoints and should be a requirement for future studies to further refine information on exercise prescription in the setting of oncology.

Importantly, despite strong theoretical and biological rationale, the evidence supporting the effects of exercise on treatment efficacy is preliminary. Future research in this area requires large-scale trials, utilizing validated outcomes of treatment efficacy (i.e. relative dose intensity for chemotherapy) in addition to attempting to identify mechanisms and predictors of improvement treatment efficacy. Such research efforts could also be directed to other cancer-specific therapies in addition to the initial reports on exercise and chemotherapy response.

As discussed in Chap. 4, an important area of consideration is the effects of exercise on cancer/tumour biology. Recent reviews have highlighted the preclinical evidence demonstrating strong promise of exercise to enhance blood perfusion of tumours, enhance immune recognition and immune cell infiltration to tumours and regulate tumour signalling and metabolism [73, 109–111]. This is an exciting area for the field; however, these concepts have yet to be examined in humans. Thus, there is a strong and urgent need for clinical studies of exercise and tumour physiology (i.e. hypoxia and perfusion) to provide critical information on the mechanistic effects of exercise on cancer control in humans [109]. Further, this will allow for a greater understanding of the synergistic effect of exercise and anticancer therapies, along with how the exercise prescription may be modified to enhance this response.

Lastly, large randomized clinical trials are currently underway, investigating the effects of exercise on survival although limited at this stage to colon, haematological, prostate and ovarian cancer. Though these multinational trials can be challenging and time-consuming, they will be critical in furthering our understanding of how exercise may improve the quantity and quality of life in individuals with a diagnosis of cancer.

Summary

The field of exercise oncology research over the past 30+ years has consistently demonstrated the safety and efficacy of exercise on a number of endpoints in cancer patients undergoing treatment. Moreover, accumulating evidence indicates that

exercise may have a critical role in both the treatment preparation phase and during active treatment in preparing for and ameliorating treatment-related physiological and psychological impairments. As the field continues to evolve in its breath, scope and rigour, future large definitive trials will provide more conclusive information on the role of exercise in disease progression and survival.

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Chapter 6
Prehabilitation: An Emerging Standard in Exercise Oncology

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Introduction

Prehabilitation in its simplest form is treatment that prepares a patient for an upcoming physiologic stressor. More specifically, for an oncologic population, prehabilitation is defined as "a process on the cancer continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment and includes physical and psychological assessments that establish a baseline functional level, identify impairments, and provide interventions that promote physical

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and psychological health to reduce the incidence and/or severity of future impairments" [1]. Prehabilitation has been studied among various diagnostic categories, including, but not limited to, cardiac and musculoskeletal, and historically focused on exercise as the sole modality [2]. However, recent reports suggest that a multimodal approach including various therapeutic treatments alongside exercise, such as smoking cessation, nutritional supplementation, and stress reduction therapies, may be more beneficial prior to antineoplastic therapy [3]. Prehabilitation offers many opportunities to enhance patient outcomes and is an important part of the oncology care continuum.

The Cancer Care Continuum: Rationale for Rehabilitation and Exercise at the Point of Diagnosis

Cancer treatments occur over a protracted continuum of care introducing myriad side effects that negatively impact multiple body systems. The aggregate burden of treatment-related side effects causes functional decline and disablement in a large number of individuals. Exercise interventions are known to mitigate, or even prevent, many of the deleterious effects of treatments. Proactive approaches to exercise prescription are needed, ideally prior to the initiation of antineoplastic therapies, so that the individual can maintain their relative baseline functional performance.

When an individual is diagnosed with cancer, they are functioning at their normal performance levels. However, this is widely variable based on comorbidities, lifestyle behaviors, and exercise preferences. Some people may be regularly exercising or even training for sport and competition, and others may be sedentary with multiple chronic conditions that limit their activity levels. Recognizing the wide variance in performance status among individuals at baseline, there is an opportunity to leverage the preoperative time period to assess performance level and function and to make exercise recommendations or even prescribe exercise interventions that optimally prepare them for the ensuing cancer therapies. The prehabilitation episode of care provides this opportunity.

The Prehabilitation Episode of Care

The evidence for exercise throughout cancer care is overwhelmingly positive [4], and the time just before treatment may be the most favorable in terms of barriers such as treatment toxicities, inadequate energy balance, or fatigue [5]. Capitalizing on this pretreatment period requires early access to patients, careful assessment of their current functional status, and resources that support an ongoing care network. The prehabilitation episode of care will vary based on the type of cancer, the individual's needs, and the available time prior to the initiation of cancer therapies.

Receptivity of the individual and their proximity to exercise and rehabilitation services are also factors to consider in providing prehabilitation care. Survey data reveal positive patient attitudes regarding prehabilitation and recognition that there may be benefit to participation. However, a primary patient-reported concern was that this new regimen of exercise would interfere in their usual routine and challenge them in being able to prepare to start cancer treatments [6].

The prehabilitation episode of care may range from a single session where baseline measures of function are obtained and education and planning efforts are undertaken for ongoing follow-up care or may entail an episode of care for aerobic, resistive, or therapeutic exercise. Due to the differences among various types of cancers and the varying degree to which these interventions have been studied, the prehabilitation model relies on individualized care planning based on these factors. Table 6.1 outlines the evidence for prehabilitation interventions across many different cancer types and is a treatment planning resource for providers.

Gastrointestinal Cancers (Including Colon and Rectal)

Colon cancer provides the greatest breadth of program examples in the literature with an emphasis on multimodal interventions [7–10]. Controlled trials including high- and low-frequency, and high- and low-intensity, aerobic and resistance exercise, supervised and unsupervised programs, and some combination of these demonstrate benefit in GI populations. Regardless of these seemingly broad prescription parameters, a minimum dose of exercise is likely necessary as one study found that a single supervised prehabilitation exercise episode per week was not enough to improve measurable outcomes [7]. The amount of total time spent in exercise may matter more than the frequency of episodes. Overall duration of exercise in colon cancer appears to have a dose response effect [8] and evidence suggests there is a threshold dose at which exercise even decreases circulating tumor cells [11].

The evidence for exercise prescription in colorectal cancers generally supports moderate- or high-intensity exercise [12–15]. However, even study controls who participated in a lower-intensity breathing and walking intervention experienced increased endurance capacity [16]. Upon follow-up, all study participants that improved their walking capacity through in the study arm and control arm were more likely to have recovered to their baseline endurance level at 9 weeks post-surgery [10]. Typically associated with pulmonary rather than gastrointestinal cancers, breathing exercises performed regularly in gastrointestinal cancer prehabilitation exercise programs are associated with reduced postoperative pulmonary complications [17–20]. This exemplifies the importance of a structured, progressive program regardless of the individual's baseline level of endurance.

Many studies use the 6-min walk test (6MWT) as the outcome measure for functional exercise capacity, and handgrip strength is identified as a strength test with sufficient evidences to be recommended in clinical practice [10, 16, 21–24].

Table 6.1 Review of prehabilitation evidence recommendations

Author, year	Article type	Cancer type (*n*)	Exercise recommendation	Setting (if specified)	End points and outcomes
Sebio Garcia, 2016 [40]	RCT	Lung cancer ($n = 22$)	***Endurance training:*** T: cycling on a cycle ergometer I: HIIT (1 min at 80% of Wpeak plus 4 min at 50% of Wpeak) D: 30 min (with 5 min warm-up and 4 min cool down) ***Resistance training*** T: major muscle groups with Thera-Bands and bodyweight exercises (6 exercises) V: 3 sets of 15 reps I: moderate perceived rate of exhaustion according to the OMNI-Resistance Scale P: from the tenth onward, the number of repetitions ***Others*** ***Breathing exercises*** using a spirometer (2×/day)	Hospital-based Supervised	***Physical results:*** *CCET, seconds ± SD* IG: +396.6 ± 197.9 ($p < 0.001$) (baseline, after intervention) IG: +226.0 ± 269.4 vs. CG: 137.8 ± 221.7 ($p = 0.005$) (baseline, postop month 3) *6MWT (m)* IG: +1.88 ± 34.7 vs. CG: −31.5 ± 64.6 ($p = 0.186$) (baseline, postop month 3) *Arm curl (no. repet)* IG: +2.9 ± 2.1 ($p = 0.002$) (baseline, after intervention) IG: +1.8 ± 3.5 vs. CG: 1.8 ± 3.5 ($p = 0.045$) (baseline, postop month 3) *30 s Chair-to-stand test (no. repet)* IG: +0.9 ± 1.2 ($p = 0.041$) (baseline, after intervention) IG: +2 ± 2.2 vs. CG: 1.3 ± 1.8 ($p = 0.002$) (baseline, postop month 3) ***Postoperative results*** *LOS, days* IG: 2 vs. CG: 3 ($p = 0.539$) *Postoperative pulmonary complications*, Melbourne Group Scale (score ≥1), *n* (%) IG: 5 (50) vs. CG: 8 (66) ($p = 0.361$)

Morano, 2013 [42]	RCT	Lung cancer ($n = 24$)	***Endurance training:*** T: walking on a treadmill I: 80% of the max workload D: 10 min increasing to 30 min ***Resistance training*** T: upper limbs with proprioceptive neuromuscular facilitation method V: 15 rep/min I: NR P: the initial load is 500 g, with an increase of 500 g each min ***Inspiratory muscle training*** (10–30 min), flexibility, stretching, and balance exercises	Hospital-based Supervised	***Physical results:*** *6 MWD*, m ± SD (baseline, week 4) IG: +49.5 ($p < 0.001$) CG: −4.6 ($p = 0.75$) ***Postoperative results*** *LOS*, days ± SD IG: 7.8 ± 4.8 vs. CG: 12.2 ± 3.6 ($p = 0.04$) *Postoperative pulmonary complications*, *n* (%) IG: 2 (16.7) vs. CG: 7 (77) ($p = 0.01$) *Days with chest tube*s, days ± SD IG: 4.5 ± 2.9 vs. CG: 7.4 ± 2.6 ($p = 0.03$) *Pneumonia*, *n* (%) IG: 0 (0) vs. CG:2 (22.2) ($p = 0.17$) Ventilation >48 h, *n* (%) IG: 1 (8.3) vs. 3 (33.3) ($p = 0.20$) *Bronchopleural fistula*, *n* (%) IG: 2 (16.7) vs. 7 (77.8) ($p = 0.009$) *Atelectasis*, *n* (%) IG: 0 (0) vs. CG: 3 (33.3) ($p = 0.06$) *Bronchospasm*, *n* (%) IG: 0 (0) vs. CG: 6 (66) ($p = 0.002$)
Benzo, 2011 [41]	RCT	Lung cancer ($n = 9$)	4 weeks of preoperative PR using the *current ACSM guidelines for exercise prescription*	Hospital-based Supervised	*Outcomes* *Hospital length of stay*, *postoperative pulmonary complications* (pneumonia (new infiltrate + either fever (>38.5 C) and white cell count >11,000 or fever and purulent secretions), *severe atelectasis* (requiring bronchoscopy), *prolonged chest tubes* (>7 days), and *prolonged mechanical ventilation* (>24 h)) No differences were found between the arms in any outcome

(continued)

Table 6.1 (continued)

Author, year	Article type	Cancer type (*n*)	Exercise recommendation	Setting (if specified)	End points and outcomes
Benzo, 2011 [41] (one article, two studies)	RCT	Lung cancer ($n = 19$)	A ten-session preoperative PR that used the following protocol: *Lower extremity (LE) endurance training* had a target time of 20 min and was performed on a treadmill or NuStep *Upper extremity (UE) endurance* was performed by arm-R-size exercises or the use of an arm ergometer or the NuStep *Strengthening exercises* with Thera-band were preformed alternating UE/LE every other day *Inspiratory muscle training (IMT)* was performed using the Threshold Inspiratory Muscle Trainer (IMT) or the P-Flex valve with a goal of 15–20 min of daily use *Incentive spirometry training* used a protocol that was reported to be associated with decreased postoperative atelectasis after thoracic surgery (18) *Slow breathing* (prolonging expiratory time and thereby decreasing respiratory rate to less than 10 breaths per min) was routinely included	Hospital-based Supervised	*Outcomes* *The frequency of open thoracotomies*: no differences *Pneumonectomy*: no differences *Days needing a chest tube* IG: 7.9 vs. CG: 9.0 ($p = 0.03$) *Incidence of prolonged chest tubes (>7 days)*: IG: 11% vs. CG: 63% ($p = 0.03$) *Hospital length of stay* IG: 6.4 vs. CG: 11.1 ($p = 0.058$) *Improvements of the shuttle walk:* Baseline vs. end point: no difference

Licker, 2017 [73]	RCT	NSCLC (n = 151)	**HIIT** T: cycle ergometer I: 5-min warm-up (50% peakWR) two 10-min series of 15-s sprint intervals (at 80–100% peakWR) interspersed by 15-s pauses and a 4-min rest between the two series 5-min cool down (an active recovery period at 30% peakWR) F: two to three times a week **Additional exercises:** Leg press, leg extension, back extension, seat row, biceps curls, or chest and shoulder press were proposed on an individual basis	Hospital-based Supervised	***Primary Outcome*** **Postoperative mortality-morbidity end point** IG: 27 (35.5%) vs. CG: 39 (50.6%) (relative risk = 0.70, 95% confidence interval [CI]: 0.48–1.02) (p = 0.080) **30-day mortality** IG: 2 (2.6) vs. CG: 2 (2.7) (p = 0.640) **At least one postoperative complication** IG: 27 (35.5%) vs. CG: 39 (50.6%) (p = 0.080) **Postoperative pulmonary complications** IG: 23% vs.CG: 44% (p = 0.018) **Rate of atelectasis** IG: 12.2% vs. CG: 36.4% (p < 0.001) **Length of stay in the post-anesthesia care unit** IG: median −7 h, IQR25–75% = −4 to −10, shorter than CG ***Second outcomes:*** During the preoperative waiting period (median 25 days) **The peak oxygen consumption** IG: **increased**, median +15%, interquartile range, 25th to 75 percentile [IQR25–75%, %] = +9% to +22% (p = 0.003) CG: **declined** (median −8%, IQR25–75% = −16% to 0%) (p = 0.005) **The 6-min walking distance** IG: **increased,** median +15%, IQR25–75% = +8% to +28% (p < 0.001)

(continued)

Table 6.1 (continued)

Author, year	Article type	Cancer type (*n*)	Exercise recommendation	Setting (if specified)	End points and outcomes
Lai, 2017 [44]	RCT	Lung cancer ($n = 60$)	**Endurance training** T: NuStep device I: NR D: 30 min daily **Inspiratory muscle training (IMT)** *Abdominal breathing training:* twice per day at 15 to 20 min each *Expiration exercise:* A simple respiratory training device. 3 times per day for 20 min each	Hospital-based Supervised	*Outcomes:* **The mean postoperative length of stay** IG: 6.9 ± 4.4 vs.CG: 10.7 ± 6.4 ($p = 0.010$) **6-MWD** IG: 28.6 ± 18.2 vs. CG: 9.4 ± 27.0 m; between-groups difference: 19.2 m ($p = 0.029$) **PEF** IG: 26.2 ± 22.5 vs. CG: 8.2 ± 10.3 L/min; between-groups difference: 18.0 L/min ($p < 0.001$) **Thirty-day PPCs** IG: 4 (13.3%) vs. CG: 11 (36.7%) ($p = 0.037$) **No differences:** Other PFT indexes, including forced vital capacity, forced expiratory volume in 1 s and diffusion capacity of the lung for carbon monoxide Global QoL, emotional function, the dyspnea score
Stefanelli, 2013 [74]	RCT	NSCLC with COPD ($n = 40$)	**Pulmonary rehabilitation program:** T: treadmill and ergometric bicycle I: a high intensity (70% of the maximum score reached at the CPET and increased by 10 W when the patient was able to tolerate the set load for 30 min) D: 3 h per session, total of 15 session in 3 week **Respiratory exercises** on the bench, mattress pad and wall bars, respectively	Hospital-based Supervised	*Peak* VO_2 IG: **improves significantly** from T0 to T1: 14.9 ± 2.3–17.8 ± 2.1 ml/kg/min ± standard deviation (SD), $p < 0.001$ (64.5 ± 16.5–76.1 ± 14.9% predicted ± SD, $p < 0.05$) and **deteriorates** from T1 to T2: 17.8 ± 2.1–15.1 ± 2.4, $p < 0.001$ (76.1 ± 14.9–64.6 ± 15.5, $p < 0.05$), **reverting to a similar value** to that at T0 CG: n**o change** from T0 to T1 and **significantly deteriorates** from T1 to T2: 14.5 ± 1.2–11.4 ± 1.2 ml/kg/min ± SD, $p < 0.00001$ (60.6 ± 8.4–47.4 ± 6.9% predicted ± SD, $p < 0.00001$)

Pehlivan, 2011 [75]	RCT	Lung cancer ($n = 60$)	**IG:** walking exercise, chest physiotherapy Length of intervention prior to surgery: 1 week Frequency: 3/week **Both IG and CG group had a postoperative pulmonary physical therapy**	Supervised-hospital exercise	***Primary outcomes:*** **The hospital stay (days)** IG: 5.40 ± 2.67 vs. CG: 9.66 ± 3.09 ($p < 0.001$) **Peripheral blood oxygen saturation:** Higher in IG ($p = 0.008$) **At least one complication:** IG: 2 (6.7%) vs. CG: 5 (16.7%) ($p = 0.04$) **Pulmonary function before surgery:** No significant differences
Kim, 2009 [76]	RCT	Colon cancer ($n = 21$)	**Aerobic exercise training** T: cycle ergometer Length of intervention prior surgery: 4 week Intensity: 40–65% of HRR, 11–16 RPE of Borg scale Frequency: 7/week Duration: 20–30 min	Home-based exercise	***The maximal measure*** **Peak power output** was responsive to training [26 ± 27%, Effects Size (ES) = 0.24; Standardized Response Mean (SRM) = 1.05; $p < 0.05$]. ***The submaximal measures*** **Heart rate and oxygen uptake** during submaximal exercise was most responsive to training (decrease by 13% ± 15%, ES = −0.24; SRM = −0.57; and 7% ± 6%, ES = −0.40; SRM −0.97; $p < 0.05$) at an exercise intensity of 76 ± 47 W There was **no change** to maximal or submaximal measures **in the control group** **The distance walked over 6 min** improved in both groups (by approximately 30 m), but the effect size and t-statistic were higher in the exercise group

(continued)

Table 6.1 (continued)

Author, year	Article type	Cancer type (*n*)	Exercise recommendation	Setting (if specified)	End points and outcomes
Gillis, 2014 [22]	RCT	Colorectal cancer (*n* = 77)	***Endurance training*** T:Walking/Running/Swimming/Cycling I: 40% of heart rate reserve D: 20 min ***Resistance training*** T: major muscle groups with Thera-Bands (8 exercises) V: 1 set of 8–12 reps I: Borg ≥12 P: resistance ↑ if Borg ≤12 or the participant could complete 15 reps ***Others*** Nutrition intervention (Whey protein), reduction anxiety	Home-based Unsupervised	***Physical results:*** *6MWD*, m ± SD IG = +25.2 ± 50.2 vs. CG = −16.4 ± 46.0 ($p < 0.001$) (baseline, week 4) IG = +23.4 ± 54.8 vs. CG = −21.8 ± 80.7 ($p = 0.020$) (baseline, postop week 8) *SF-36* (baseline, week 4, postop week 4, postop week 8) IG vs. CG: NS for all domains ***Postoperative results*** *LOS, days* [interquartile range] IG: 4 [3–6] vs. CG: 5 [3–9] ($p = 0.446$) *Postoperative complications*, Clavien-Dindo (grade ≥1), *n* (%) IG: 7 (19) vs. CG: 12 (30) ($p = 0.506$) *30-day emergency department visit*, *n* (%) IG: 6 (16) vs. CG: 9 (23) ($p = 420$) *30-day readmission*, *n* (%) IG: 6 (15) vs. CG: 5 (13) ($p = 0.780$)

Li, 2013 [10]	Case-control	Colorectal cancer ($n = 87$)	**Moderate aerobic exercise** T: an aerobic exercise machine D: 30 min three times a week I: 50% maximal HR (220—age) **Resistance exercises** Use calisthenics and elastic band movements, three times a week to volitional fatigue **Other intervention:** Breathing exercises Nutritional assessment Protein supplementation Anxiety reduction	Home-based exercise	*Primary outcomes* **6MWT** Functional walking capacity improved by 40 ± 40 m ($p < 0.01$) during the prehabilitation period. The patients in the prehabilitation program had better postoperative walking capacity at both 4 weeks (mean difference, 51.5 ± 93 m; $p < 0.01$) and 8 weeks (mean difference, 84.5 ± 83 m; $p < 0.01$) *Second outcomes* **Postoperative complications** **QoL indicators** **LOS** Self-reported activity data did not demonstrate clinical or statistical difference of the intervention LOS and complications rates were similar in both groups
Dunne, 2016 [77]	RCT	Colorectal cancer with liver metastasis ($n = 37$)	**Prehabilitation exercise** T: cycle ergometer D: 12 interval exercise sessions over a 4-week period. I: 30 min of interval training alternating between exercise of moderate (less than 60% VO_2 at peak exercise) and vigorous (more than 90% VO_2 at peak) intensity (include a warm-up and warm-down) Others: two recovery exercise sessions were included at the end of the first and fourth weeks (sessions 3 and 12)	Hospital-supervised exercise	***Primary outcomes:*** **CPET-derived AT, pVO$_2$** ***Secondary outcomes:*** **Changes in preoperative CPET parameters, QoL indicators** Prehabilitation program achieved its primary objective of a 1·5 mL kg^{-1} min^{-1} improvement in VO_2 at AT, in comparison with standard care Intervention was associated with improvements in overall QoL and mental health scores ($p < 0.05$). There was also a trend toward improved physical health ($p = 0.1$)

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Table 6.1 (continued)

Author, year	Article type	Cancer type (*n*)	Exercise recommendation	Setting (if specified)	End points and outcomes
Bosquet -Dion, 2018 [7]	RCT	Colorectal cancer (*n* = 80)	***Preoperative exercise*** **Home-based aerobic exercise** T: walking, cycling or jogging D: 30 min, 3–4 days per week, I: moderate-intensity aerobic activity (60–70% of maximal HR) **Resistance training** Eight exercises targeting major muscle groups of the core, upper and lower limbs and to be performed 3–4 times per week in up to two sets of a range of 8–15 repetitions, dependent on volitional fatigue. Patients were given an elastic resistance band, as well as a pedometer **The supervised aerobic exercise and resistance training**: 30 min of moderate aerobic exercise, including a 5-min warm-up, and 25 min of resistance exercises on treadmill, followed by 5 min of stretching. Resistant intensity is progressed when patients could complete the routine with perceived mild exertion (defined as 12 or less on the 20 point Borg scale) **Other intervention:** **In-hospital exercise after surgery, nutritional intervention, anxiety-reduction strategies**	Home-based and supervised exercise during preoperative phase and in-hospital exercise during the postoperative phase	**Outcomes:** After surgery, changes in 6MWD were also similar in both groups. In IG, however, there was a significant association between physical activity energy expenditure and 6MWD ($p < 0.01$). Previously inactive patients were more likely to improve functional capacity due to prehabilitation (OR 7.07 [95% CI 1.10–45.51])

Chen, 2017 [21]	RCT	Colorectal cancer (n = 116)	***Prehabilitation intervention*** **Aerobic exercise** D: 20 min, three times per week T: their own preferred I: 50% age-predicted maximal HR (220—age) **Resistance exercise** D: 20 min, followed aerobic exercise T: elastic resistance band, targeting major muscle groups I: 8–12 repetitions maximum Other intervention: Nutrition, relaxation and breathing exercises to reduce anxiety		**Outcomes** Over the preoperative period, the amount of moderate- and vigorous-intensity physical activities significantly increased in IG. And patients in IG also demonstrated a greater improvement in 6MWT. At the time of surgery, a greater proportion of patients in PREHAB met current physical activity guidelines
West, 2015 [78]	Case-control	Rectal cancer (n = 35)	**Supervised interval training** T: electromagnetically braked cycle ergometer D: 40 min (including 5 min warm-up and 5 min cool-down) of interval training, 6 week, three sessions/week I: Moderate to severe intensities (total 20 min) for the first two sessions, then increased to 40 min (6 × 3 min intervals at moderate intensity and 6 × 2 min intervals at severe intensity)	Hospital-supervised exercise	***Primary outcomes:*** **CPET-derived AT** ***Secondary outcomes:*** **CPET-derived pVO_2** Peak VO_2 and AT fell in all patients adversely affected by nCRT **IG:** peak VO_2 and AT improved by (+2.1 mL kg^{-1} min^{-1}; 95% CI, +1.3 to +2.9; p = 0.0001) **CG:** peak VO_2 and AT remained unchanged

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Table 6.1 (continued)

Author, year	Article type	Cancer type (*n*)	Exercise recommendation	Setting (if specified)	End points and outcomes
Singh, 2017 [79]	Single group (self-control)	Rectal cancer ($n = 12$)	The exercise program includes 2 60-min supervised sessions per week over a period of ~16 weeks before surgery In addition, a home-based activity log sheet, at least 2 × 15 min or more per week, 150 min per week **Supervised sessions**: *Progressive resistance training:* Use standard resistance training machine equipment Major muscle groups of the upper and lower body and included the chest press, seated row, latissimus pull-down, leg extension, leg curl, and leg press exercises Participants performed 2–4 sets per exercise at a 6–12 repetition maximum (RM) intensity ***Aerobic exercise*** T: walking or jogging on a treadmill and cycling or rowing on a stationary ergometer D: 20 min I: 60–80% of estimated maximum heart rate	Weekly Supervised-hospital exercise and a home-based activity log sheet	Muscle strength improved 9–29% at pre-surgery, although this was not statistically significant and declined post-surgery ($p < 0.05$). Post-surgery strength levels were comparable with pretraining levels Lean mass was preserved at pre-surgery despite neoadjuvant chemoradiation treatment, whereas post-surgery lean mass decreased ($p < 0.05$) compared with baseline (−3.2 5.4 kg) and pre-surgery (−3.7 5.4 kg) There were no substantial changes in quality of life or fatigue

Yamana, 2015 [80]	RCT	Esophageal cancer ($n = 60$)	***Endurance training:*** T: cycling on a cycle ergometer I: NR D: 20 min ***Resistance training*** T: lower limbs and abdominal muscles with a weight V: NR I: NR P: NR ***Respiratory exercises:*** respiratory muscle and thoracic cage stretching Deep inspiration	Hospital-based Supervised	*Postoperative pulmonary complications*, *Clavien-Dindo* (grade ≥1), *n* (%) IG: 8 (27) vs. CG: 18 (60) ($p = 0.014$) *Postoperative pulmonary complications*, UPSS (Score ≥1), *n* (%) POD1: IG = 10 (33); CG = 17(63); $p = 0.031$ POD2: IG = 22 (73); CG = 19 (63); $p = 0.87$ POD3: IG = 22 (73); CG = 15 (50); $p = 0.13$ POD4: IG = 6 (20); CG = 8 (27); $p = 0.51$
Dronkers, 2010 [81]	RCT	Abdominal cancers ($n = 42$)	Hospital-supervised exercise, twice a week, lasted 60 min every session, when waiting for surgery (2–4 weeks) **Resistance training of the lower limb extensors** (with a maximum of one set of 8–15 rm, consistent with 60–80% of the one-repetition maximum 18–21); **Inspiratory muscle training**: patients breathed against a variable resistance (10–60% of the maximal inspiratory pressure) for about 15 min (240 breathing cycles); **Aerobic training**: T: walking or cycling I: a moderate intensity (to 55–75% of maximal heart rate) or perceived exertion (between 11 and 13 on the Borg scale) D: lasted 20–30 min **Training functional activities** according to the patients' capabilities and interest **Daily walking and breathing exercises (do the same in CG)**	Hospital-supervised twice-weekly and home-based exercise	***Primary outcome:*** **Maximum aerobic capacity** No difference **Strength and power of lower limb muscles** No difference **Respiratory muscle endurance increased in the preoperative period** IG: 259 ± 273 to 404 ± 349 vs. CG: 350 ± 299 to 305 ± 323, ($p < 0.01$) **Functional mobility** **QoL assessment** **Fatigue assessment** No significant differences revealed ***Secondary outcome:*** **Postoperative complications** No significant difference

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Table 6.1 (continued)

Author, year	Article type	Cancer type (*n*)	Exercise recommendation	Setting (if specified)	End points and outcomes
Huang, 2016 [82]	Cohort study	GI cancer ($n = 26$)	**Exercise program, 3–5 times weekly** **Aerobic training** I: 60–80% of the maximum heart rate at peak VO_2 D: 30–45 min **Strength training**	Hospital-supervised and home-based exercise	***Primary outcomes:*** **CPET-derived AT and pVO_2** **Oxygen uptake at anaerobic threshold (AT)** Baseline: 10.4 vs. After exercise before surgery: 11.6 ml kg^{-1} min^{-1} ($\Delta AT = 1.2 \pm 3.0$ ml kg^{-1} min^{-1} [9%]; $p = 0.046$) **Peak oxygen uptake (pVO_2)** Baseline: 16.0 vs. After exercise before surgery: 17.7 ml kg^{-1} min^{-1} ($\Delta pVO_2 = 1.7 \pm 2.4$ ml kg^{-1} min^{-1} [9%]; $p = 0.002$); and pVO_2/BSA from 658 to 726 ml min^{-1} m^{-2}; (ΔpVO_2/BSA = 68 ± 112.3 mL min^{-1} m^2 [10%]; $p = 0.004$) But only 50% of the cohort responded ***Secondary outcomes***: postoperative morbidity No difference

Cho, 2014 [83]	Cohort study	Gastric cancer (stage I, $n = 72$)	**Preoperative training program was performed within 7 days after completing 4 weeks of the protocol exercise as followed:** **Aerobic training** T: a treadmill or bicycle ergometer, swimming, dancing, or jogging D: 3–7 days per week **Strength training** I: 30 kcal/kg/week. Maximal heart rate reserve or the Borg scale to rate the level of perceived exertion D: once or twice per week **Stretching** Before and after the aerobic training		***Primary outcomes:*** **Postoperative complications** IG: 1 vs. CG 22, ($p = 0.008$) **LOS** IG: 9.0 vs. CG: 10.0 days ($p = 0.038$) ***Secondary outcomes*** **Volume of visceral fat before operation** IG: −34.8 (−64.7 to −4.9) ($p = 0.025$) **Body weight before operation** IG: −0.48 (−0.79 to −0.18) ($p = 0.004$)

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Table 6.1 (continued)

Author, year	Article type	Cancer type (*n*)	Exercise recommendation	Setting (if specified)	End points and outcomes
Jensen, 2014 [84]	RCT	Urological cancers (*n* = 107, IG = 50, CG = 57)	**Length of intervention:** 2 weeks **Frequency:** 2×/day **Endurance training** T: lower limbs on step trainer I: NR D: 15 min **Resistance training** T: muscle groups involved in activities such as mobilization, in and out of bed, chair raise performance, stair climbing, and gait speed (6 exercises) V: 1 set of 10–15 reps to start I: NR P: ↑ number of exercise reps through the training program	Home-based exercise	The intervention group significantly improved HRQoL scores in dyspnea, constipation, and abdominal flatulence compared to the standard group. In contrast, the standard group reported significantly reduced symptoms in sleeping pattern and clinically relevant differences in role function, body function, and fatigue. The intervention did not compromise inpatient satisfaction **Symptom scales** Dyspnea IG: −7.0 (−15.5 to 1.6) vs. CG: 2.6 (−4.4 to 9.6), ($p = 0.05$) Insomnia IG: 6.4 (−4.5 to 17.2) vs. CG: −7.8 (−17.4 to 1.6), ($p = 0.04$) Constipation IG: 1.6 (5.7–8.8) vs. CG: 14.4 (6.4–22.4), ($p = 0.02$) **Disease-specific scales (BLM30, BLS24)** Abdominal flatulence IG: 4.3 (−3.6 to 12.1) vs. CG: 10.7 (3.0–18.3), ($p = 0.05$) **Single timepoint post-surgery** Urinary problems (only neobladders) IG: 18.1 (5.3–30.9) vs. CG: 38.3 (19.4–57.0), ($p = 0.05$)

Jensen, 2015 [85]	RCT	Bladder cancer (n = 107)	**Length of intervention:** 2 weeks **Frequency:** 2×/day **Endurance training** T: lower limbs on step trainer I: NR D: 15 min **Resistance training** T: muscle groups involved in activities such as mobilization, in and out of bed, chair raise performance, stair climbing, and gait speed (6 exercises) V: 1 set of 10–15 reps to start I: NR P: ↑ number of exercise reps through the training program	Home-based Unsupervised	***Postoperative outcomes*** **LOS, days [range]** IG: 8 [3–30] vs. CG: 8 [4–55] (p = 0.68) **PC, Clavien-Dindo (grade ≥1), *n* (%)** IG: 30 (60) vs. CG: 34 (60) (p = 0.64) **30-day readmission, *n* (%)** IG: 13 (30) vs. CG: 12 (23) (p = 0.49) **90-day mortality, *n* (%)** IG: 3 (6) vs. CG: 4 (7) (p = 0.84)
Banerjee, 2013 [86]	RCT	Bladder cancer (n = 63)	Supervised exercise sessions preoperatively twice weekly for 4 weeks		Average VO_2 max (ml/kg/min) IG: 20.38 vs. CG: 25.5 (p = 0.002)
Jensen, 2016 [87]	RCT	Bladder cancer (n = 107)	***Endurance training*** T: lower limbs on step trainer I: NR D: 15 min ***Resistance training*** T: muscle groups involved in activities such as mobilization, in and out of bed, chair raise performance, stair climbing, and gait speed (6 exercises) V: 1 set of 10–15 reps to start I: NR P: ↑ number of exercise repetitions through the training program	Home-based Unsupervised	***Physical results:*** *Muscle leg power test*, W/kg (95% CI) (baseline, week 2) IG: +0.35 (0.12;0.54) (p < 0.002) CG: +0.03 (1.78; 2.22) (p = 0.48) IG vs. CG (p < 0.006)

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Table 6.1 (continued)

Author, year	Article type	Cancer type (*n*)	Exercise recommendation	Setting (if specified)	End points and outcomes
Santa Mina, 2018 [52]	RCT	Prostate cancer (waiting for radical prostatectomy), *n* = 86	**Prehab aerobic exercise:** T: individualized, total-body exercise D: 60 min, 3–4 days per week I: moderate-intensity exercise Other exercise: **Daily pelvic floor muscle exercises**	Unsupervised, home-based	**Outcomes:** After the intervention and prior to surgery, PREHAB participants demonstrated less **anxiety** ($p = 0.035$) and decreased **body fat percentage** ($p = 0.001$) compared to CON Four weeks postoperatively, PREHAB participants had greater **6MWT scores** of clinical significance compared to CON ($p = 0.006$) Finally, compared to CON, **grip strength** and **anxiety** were also greater in the PREHAB at 26 weeks ($p = 0.022$) and ($p = 0.025$), respectively
Centemero, 2010 [55]	RCT	Prostate cancer (*n* = 118)	**IG: preoperative and postoperative pelvic muscle exercises** Length of intervention prior to surgery: 30 days Intensity: maximal and submaximal contractions Frequency: 7/week Duration: 2/week for 30 min with physiologist supervised, 7/week for 30 min at home **CG: postoperative pelvic muscle exercises**	Supervised hospital exercise and home-based exercise	**Rate of return to continence** 3 month, IG: 59.3% (35 of 59) vs. CG 37.3% (22 of 59) ($p = 0.028$) **QoL: ICS male SF mean score** 1 month: IG: 14.6 vs. CG: 18.3 ($p = 0.002$) 3 months: IG: 8.1 vs. CG: 12.2 ($p = 0.002$) **Regression analyses** Preoperative PFME had a 0.41-fold lower risk of being incontinent 1 month after RP and a 0.38-fold lower risk of being incontinent 3 month after RP ($p < 0.001$)

Bales, 2000 [88]	RCT	Prostate cancer (n = 100)	**Graded pelvic muscle exercise training with biofeedback** Length of intervention prior to surgery: 2–4 weeks Intensity: 5–10 s contraction, 10–15 reps Frequency: 7/week Duration: 4/day	Supervised hospital exercise	**Rate of return to continence rates** IG: 94% (44 of 47) vs. CG: 96% (48 of 50) (p = 0.596). Also, at 1, 2, 3, and 4 months after surgery, there was no significantly difference between the two groups
Burgio, 2006 [89]	RCT	Prostate cancer (n = 125)	**Pelvic muscle exercise, biofeedback-assisted behavioral training** Length of intervention prior to surgery: 1 week Intensity: 10 s contractions, 10 s relaxations Frequency: 7/week Duration: 3 sessions of 15 exercises/day	Home-based exercise	**Urethral length preserved** IG: 85.2% vs. CG: 98.0% (p = 0.03) **Severe/continual leakage at the 6-month end point** IG: 5.9% vs. CG: 19.6% (p = 0.04) **Self-reported urine loss with coughing** IG: 22.0% vs. CG: 51.1% (p = 0.003) **Self-reported urine loss with sneezing** IG: 26.0% vs. CG: 48.9% (p = 0.02) **Self-reported urine loss with getting up from lying down** IG: 14.0% vs. CG: 31.9% (p = 0.04) **No differences were found on return to work and usual activities or quality of life measures**
Rao, 2012 [90]	Pilot RCT	Breast cancer (n = 10)	**IG** exercise boot camp program+ neoadjuvant chemotherap**y** Boot camp program T: combined circuit-based activities such as jumping jacks, running in place, arm and leg work with exercise balls, bands, and weights up to 5 pounds I: individual tolerance levels D: 60 min F: 3/week × 4–6 months **CG** Neoadjuvant chemotherapy	Supervised, home-based exercise	Mean BMI IG: 28.0 vs. CG: 35.8 (p = 0.03) No significant difference of tumor characteristics (including Ki-67 in the tumor, size, axillary, lymph node status, insulin growth factor 1 (IGF-1), C-peptide levels) and clinical and pathologic response to neoadjuvant chemotherapy at breast and axillary site

The GI prehabilitation literature emphasizes trimodal prehabilitation programs that include exercise, nutrition, and stress and anxiety management interventions [14]. The impact of prehabilitation exercise is improved with the trimodal program approach suggesting the importance of a comprehensive and interdisciplinary approach [10]. The combination of prehabilitation exercise with supplemental whey protein attenuated loss of lean body mass, thus protecting muscle and preventing sarcopenia [25]. Less is known about the anxiety reduction components of prehabilitation, but exercise in general has been shown to reduce anxiety in chronic illness [26]. As such, education on proper nutrition and anxiety reduction techniques as a part of a multimodal prehabilitation approach may serve to enhance the beneficial effect of exercise before treatment.

A consensus surgical opinion paper endorses prehabilitation as preferred care for elderly colorectal cancer patients [27]. While modifying time to surgical resection in favor of more exercise is not typically recommended, overall time from early-stage colorectal cancer diagnosis to surgical intervention may not impact overall 5-year survival [28]. Median time from diagnosis to surgery was 53 days in this study allowing for at least 4 weeks of exercise intervention depending on access. Current trends favor prehabilitation exercise as a component of surgical planning specifically highlighted in the Enhanced Recovery After Surgery (ERAS) protocols and literature [7, 9, 29].

Lung Cancer

Lung cancer is one of the most commonly diagnosed cancers among men and women in the United States. Individuals diagnosed with lung cancer tend to have lower performance status at baseline compared to other cancer diagnoses with more comorbidities and greater utilization of health-care services leading up to diagnosis [30, 31]. Additionally, lung cancers tend to be diagnosed at later stages of disease. These factors contribute to a high number of patients being deemed as poor surgical candidates at the point of diagnosis. Recent advances in lung cancer screening however, using low-dose computed tomography, are increasing the number of cancers identified at the early stage of the disease [32], likely increasing the number of patients who could be candidates for surgical resection. Prehabilitation exercise programs may improve operative risk status with exercise as pulmonary function and walking tolerance is improved [33]. This makes prehabilitation care even more critical as more lung cancers are diagnosed at earlier stages [34].

Individuals with inoperable lung tumors are commonly prescribed chemotherapy as first-line antineoplastic treatment to reduce the tumor burden and ideally enable them to qualify for surgery. When exercise is offered concurrently with chemotherapy, the improvements in pulmonary function further improve opportunity to achieve status for the surgical intervention, offering the potential for greater disease-free survival [35]. Progressive aerobic and resistance exercise during chemotherapy can improve aerobic capacity, strength, functional capacity, and emotional wellbeing

[36]. This group exercise program was a 90-min, twice weekly supervised session for whole-body strength and conditioning that included progressive resistive exercise and aerobic training on stationary bikes at 85–95% maximum heart rate [36].

Although study enrollment numbers are relatively small, outcomes show significant benefit in lung function from prehabilitation exercise programs in as little as 2 weeks before lung resection surgery [37]. Even in individuals with more severely compromised lung capacity, such as those with chronic obstructive pulmonary disease (COPD) and lung cancer, lung function can be improved with exercise. Additionally, health-care utilization end points such as time to postoperative hospital discharge, need for tracheostomy, and need for prolonged oxygen inhalation can be improved [38, 39]. Additional trials have shown positive impact on hospital length of stay and inpatient complication rates in lung cancer surgeries when prehabilitation exercise is prescribed [40, 41]. Evidence suggests that greater frequency and duration of the prehabilitation exercise program not only had greater physiological benefit but reduces cost, health-care utilization, and adverse event outcomes [42–45].

Additional considerations with the lung cancer population include the prevalence of tobacco use. At diagnosis many individuals may be current smokers or trying to quit. These individuals are often sedentary and demonstrate dyspnea with low levels of exertion likely contributing to activity avoidance [46]. Compelling evidence suggests that an individual's dyspnea symptoms can guide the progression of a strength and aerobic training program and may help to promote adherence to an exercise program, reduce symptoms with activity, and improve pulmonary function [47]. In this trial, Coats and colleagues [47] reduced training intensity using a dyspnea Borg score threshold ≥ 6. Interestingly, this study recruited and enrolled patients undergoing work-up for (but not officially diagnosed with) lung cancer. The work-up for a lung cancer diagnosis can take several weeks for adequate testing and diagnosis confirmation. Of the 72 eligible patients, 71 were eventually confirmed to have cancer and the majority had already enrolled in the exercise trial. Given the exceptionally favorable benefit of exercise, intervention even before final diagnosis may be considered as a clinical strategy in the diagnostic work-up for lung cancer.

The impact of the prehabilitation program in lung cancer is magnified when it is accompanied by a transition to postoperative rehabilitation interventions [48]. Exercise interventions that can be performed at home not only improve pulmonary function but are effective in achieving adherence to the prescribed intervention [48]. Individually designed exercise programs are warranted to meet goals, which will vary according to the extent of disease and treatment type [49], but overall improvements in physical fitness persisted following the intervention. A recent study found that both early (14 days after resection) and late (14 weeks after resection) rehabilitation improved cardiovascular response in lung cancer [50]. Of note, the late rehabilitation group scored higher in fatigue across the exercise period. The late rehabilitation group showed improvement in fatigue after the intervention. As fatigue is a known barrier to exercise [5], the authors recommend early rehabilitation. This enhances the argument for prehabilitation in that it is better to start the exercise which treats the fatigue before the patient experiences it if possible, both to enhance compliance and achieve maximum benefit.

There are currently no published trimodal lung cancer studies, but one trial has been registered.[1] This could be due to the nature of the disease itself, the availability of these interventions to researchers, or the prevailing belief about the lack of benefits. Telerehabilitation is also being explored to improve exercise interventions with lung cancer as it may remove some of the traditional barriers to exercise. A recent study using a home-based virtual reality program with non-small cell lung cancer patients found an increased exercise participation [51].

Prostate Cancer

The literature is less robust with clinical trials of prehabilitation exercise interventions among men with prostate cancer. Nonetheless, evidence supports physical activity and targeted exercises preoperatively targeting pelvic floor strength and muscle function to promote restoration of continence post-prostatectomy [12]. Men who meet general physical activity guidelines are less likely to be incontinent after radical prostatectomy [52]. This association underscores the importance of exercise education and prescription at the point of diagnosis and integration of exercise as soon as possible in prostate cancer care. Part of standard care for early prostate cancer includes an intervention called *watchful waiting*. This entails ongoing monitoring of prostate-specific antigen levels prior to the initiation of antineoplastic therapies. *Watchful waiting* time periods can extend for several months prior to initiating cancer treatments, offering ample time for the initiation of exercise interventions.

Smaller randomized controlled trials that have investigated prehabilitation exercise interventions in prostate cancer identify that a home-based, moderate-intensity exercise program effectively improved 6MWD and grip strength and decreased body fat and anxiety [52]. The intervention group returned to baseline 6MWD at 4 weeks compared to 12 weeks in the control group. Grip strength was maintained in the prehabilitation group, but declined in the control group. Typical for their region, the study participants waited on average 2.5 months from diagnosis to surgery, allowing for ample time for prehabilitation [52]. Recent studies have started to investigate the feasibility of multimodal prehabilitation programs in prostate cancer with positive results regarding patient receptivity and follow-up [53].

Incontinence is commonly experienced to varying degrees following prostatectomy with pelvic floor exercises prescribed to treat this condition [54]. When these exercises are taught preoperatively, this prehabilitation episode of care improves early return to continence [12, 55].

One of the prominent challenges with prostate cancer rehabilitation is engagement of patients regarding their sexual and continence needs. Initiating conversations

[1] https://clinicaltrials.gov/ct2/show/NCT03068507

through a prehabilitation intervention, using a peer-to-peer approach, may promote better engagement and uptake of preoperative and postoperative exercises that can facilitate return to optimal function [56].

Breast Cancer

Since preoperative evidence is limited for breast cancer, postoperative studies with a preoperative component are helpful to establish an appropriate exercise program. Using a model of prospective surveillance, the identified components of a breast cancer prehabilitation program include baseline assessment of upper limb strength, range of motion and limb volume assessment, and education for postoperative exercises [57]. By providing the upper limb assessment preoperatively, there is also an opportunity to instruct patients on how to perform postoperative upper limb mobility exercises and to promote awareness of lymphedema precautions [57]. Some individuals may present with preexisting upper quadrant impairments that require an episode of care to prepare them for surgery and pending radiation therapy treatments. Initiating supervised therapeutic exercises preoperatively for this population is warranted and may improve surgical and functional outcomes postoperatively [58]. A small uncontrolled study showed no increased risk of postoperative seroma with prehabilitation shoulder exercises taught and performed before surgery [59].

Shoulder and upper quadrant exercises, while historically an area of emphasis in post-breast cancer surgery recovery, only meet a fraction of the needs of breast cancer patients. Experts argue that breast cancer patients are best served by a multimodal prehabilitation program including targeted upper body exercise, total body cardiovascular and strengthening exercise, nutrition optimization, smoking cessation, and stress reduction interventions [60]. Emerging research suggests that mind body interventions in the preoperative period may improve emotional and cognitive domains [61]. Moreover, alterations in gene expression of breast cancer tumor tissue were observed with exercise before surgery providing a possible mechanism for prehabilitation as a treatment of breast cancer [62].

Hematologic Malignancies

Survey data of patients with hematologic malignancy identifies that these individuals make substantial changes in diet, exercise, and smoking cessation after diagnosis, more so than other cancer diagnoses [63]. Hematopoietic stem cell transplant (HSCT) is a mainstay for many individuals, and emerging evidence suggests there are benefits to exercise prior to HSCT including improved endurance prior to transplant with an aerobic exercise program. Research has identified that the Borg scale correlates with the intensity of resistance and exercise tolerance after transplant suggesting this could be an important assessment tool in patients with hematologic

malignancy [64]. A meta-analysis determined that exercise had a positive effect on muscle strength, fatigue, and quality of life in this population. A subgroup analysis showed that exercise had a particularly favorable affect when started before the transplant, as in prehabilitation [65]. Prehabilitation is feasible in this time period prior to HSCT, with high adherence to exercise prescription and improved self-reported quality of life, blood count markers, and fatigue reported [66].

Comprehensive Approaches to Integrating Prehabilitation

Prehabilitation is an important part of the oncology care continuum and often involves a multimodal approach that may include such interventions as nutrition (e.g., protein supplementation), stress management strategies, and smoking cessation, in addition to exercise interventions. Prehabilitation is often utilized shortly after diagnosis and prior to the first cancer therapy intervention which is frequently a surgical procedure. As such, there have been numerous studies describing prehabilitation in a pre-surgical population using Enhanced Recovery After Surgery (ERAS) programs. These surgical protocols focus on the perioperative and early postoperative time period and aim to optimize surgical outcomes through improved health and performance status [67]. These protocols involve a variety of different interventions such as limiting intravenous fluids, managing pain, and promoting early mobilization after surgery. Prehabilitation in ERAS protocols may begin weeks before surgery and frequently includes an episode of supervised exercise, tailored to the individual's needs [68].

The current state of exercise oncology promotes exercise as a recommended intervention for all individuals diagnosed with cancer at all disease states and treatment phases for its immediate and long-term benefits in reducing multisystem symptoms and improving survival [1–8]. The American College of Sports Medicine (ACSM) published exercise guidelines for cancer patients that include general recommendations for physical activity levels as well as specific exercise prescription targeting alleviation of cancer treatment-related physical impairments [69]. These guidelines have been reaffirmed by other expert organizations around the world, affirming the assertion that every patient needs something regarding an exercise program, and for some individuals and at some timepoint in the care continuum, there is evidence for more targeted and specific recommendations [70, 71].

Specific recommendations for exercise in cancer patients continue to evolve based upon improving research. There have been increasing numbers of studies related to prehabilitation exercise in cancer patients in the past few years. Table 6.1 provides a comprehensive overview of current evidence in this growing field.

The basic principles of exercise prescription apply to the prehabilitation episode of care. Prior to initiation of an exercise program, individuals with cancer should undergo pre-screening evaluations [13]. This assessment should include consideration of the particular disease and corresponding treatments that the individual will experience, along with awareness of the anticipated side effects and late effects that

will impact the exercise intervention [10, 13]. Disease-specific evaluations are also important; for example, breast cancer patients should have arm, shoulder, and neck mobility assessments, while prostate cancer patients should be evaluated for pelvic floor function and overall muscle strength prior to initiation of cancer treatment [10, 14].

In summary, implementing the guidelines recommended by the ACSM for exercise in cancer patients in addition to other prehabilitative interventions is important. However, appropriate pre-screening of patients for oncologic and non-oncologic comorbidities is necessary in order to provide safe, effective, and appropriate prehabilitation.

Future Direction in Prehabilitation

Regarding the benefits of prehabilitation, the body of evidence continues to develop across different types of cancers. Future efforts in clinical practice and research will need to not only seek to develop the effectiveness of this intervention model but seek to improve the implementation of this model as a standard of cancer care. Ideally, research should further explore health-care cost and utilization end points that have been identified in preliminary research.

The model of prehabilitation currently focuses on optimizing pretreatment health status. However, this important intervention timepoint can also be used to leverage the information captured at baseline to develop risk stratification schema that can better direct ongoing exercise care and promote necessary information that can inform screening and assessment timepoints throughout the continuum of care using a prospective surveillance approach. Patients should be screened pretreatment, ideally at time of diagnosis, to identify areas of physical impairments and other health needs [13]. Based on the results of screening, addressing each area of functional impairment and health need can improve patient outcomes postoperatively and post-systemic treatment and radiation. There are several different published models outlining prehabilitation care [13]. The prospective surveillance model identifies impairments prior to cancer treatment and has demonstrated improved outcomes in the breast cancer populations [14]. Preoperative tailored exercise programs are a model that can be implemented to improve functional outcomes [15]. A more comprehensive model for prehabilitation is that of multimodal interventions, where a tailored exercise program is only a part of the prehabilitation program [15]. Other interventions include nutritional assessments, supportive group therapy, relaxation strategies, and objective measures of function and health [15].

Introducing exercise pretreatment has been shown to reduce functional decline, improve treatment tolerance, and improve exercise adherence [12]. However, outside of colorectal cancer, guidelines for prehabilitation care are not yet developed. Additionally, specific recommendations for the optimal timing and dose of exercise have yet to be established for prehabilitation [12].

In the lung cancer population, identified areas for research include the development of a specific exercise prehabilitation program with objective assessments of cardiopulmonary function and strength in addition to appropriate timing, duration, and intensity of training [15]. The colorectal cancer literature has research gaps related to appropriateness for frail or vulnerable patients in addition to standardization of exercise intensity, duration, and assessment tools [15]. Similarly, gaps in the prehabilitation research in breast cancer patients include screening tools, impact of prehabilitation in patients with premorbid conditions, and a standardized exercise program [15].

The research published to date on prehabilitation for cancer patients is overall supportive and demonstrates the beneficial effects for cancer patient's pretreatment. However, significant gaps remain in the prehabilitation research with regard to screening and standardization of exercise programs.

Additional barriers to integration of prehabilitation exercise for cancer patients include a lack of standardized clinical workflows that support the interface of patients at the point of diagnosis with exercise and rehabilitation professionals. Standardized baseline assessment of function and physical performance with concomitant exercise prescription should be a goal for future clinical practice. Current research efforts are underway to refine models that include a standardized assessment by a clinically integrated PT in cancer care centers [72]. This approach to care puts the exercise professional in direct interface with the patients and reduces barriers to exercise. Payment issues abound regarding supportive services such as exercise and nutrition counseling for individuals with cancer. While rehabilitation is a covered service by most public and private insurance payers, there are restrictions around medical necessity, and co-pays often create barriers to engaging in an ongoing episode of exercise care.

Summary

The functional morbidity burden associated with cancer and its treatments is prevalent with the majority of individuals experiencing at least one functional impairment and most suffering functional decline. An exercise episode of care prior to the onset of cancer treatments, known as prehabilitation, is effective in optimally preparing an individual to enter cancer treatment in a better state of fitness and health and improves outcomes.

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Chapter 7
Surgical Recovery

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What Is Postoperative Exercise?

Postoperative exercise is physical activity within the postsurgical time period; this can be defined as short term (up to 8 weeks post-op) or long term (greater than 8 weeks and/or up to 1 year post-op). Exercises include ambulation, range of motion (passive, active, active-assisted), stretching and flexibility, balance, proprioception, aerobic, and resistance. The specific type, onset, duration, and quantity will depend on each individual patient based on the surgical procedure performed and expected recovery period.

Types of Oncologic Surgery

The range of surgical interventions that can be performed in a cancer patient is extensive and ranges from minimally invasive procedures to some of the most extensive and morbid surgeries that are performed. The surgical management plan for any cancer patient depends on multiple oncologic factors (location of tumor, pathology, extent of disease) as well as patient factors (associated medical comorbidities, life expectancy, baseline physical fitness). Table 7.1 lists the most common surgeries by location.

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Table 7.1 Most common oncologic surgeries by location

Body	Location	Diagnostic/adjuvant	Definitive	Palliative
Neck				
	Thyroid	Ultrasound-guided biopsy	Thyroidectomy (partial, total), neck dissection	Tracheostomy, debridement
	Salivary glands		Superficial/total parotidectomy, minor gland removal, neck dissection	
	Mouth/ nose/ larynx	Endoscopy	Wide excision, laryngectomy (partial, total), tracheostomy, neck dissection	Tracheostomy, debridement
	Brain	Ventricular access device, ventricular peritoneal shunt	Craniotomy, transsphenoidal pituitary removal, neuroendoscopy	
Soft tissue				
	Breast	Sentinel lymph node biopsy	Partial mastectomy, mastectomy, axillary dissection	Debridement, excision
	Skin	Sentinel lymph node biopsy, lymph node dissection	Wide local excision	Debridement, excision
Thorax				
	Lung	VATS-biopsy, mediastinoscopy	Video-assisted thoracoscopic surgery (VATS), thoracotomy, lung resection (wedge, lobectomy, pneumonectomy)	Thoracentesis
	Esophagus	Endoscopy with biopsy, gastrostomy tube	Esophagectomy	Spit fistula
Abdomen				
	Stomach	Diagnostic laparoscopy, peritoneal washings	Gastrectomy (partial, total), gastrojejunostomy, esophagojejunostomy	Gastrostomy tube, jejunostomy tube
	Small bowel		Small bowel resection, ileostomy creation	Ostomy creation
	Pancreas	Diagnostic laparoscopy, endoscopy, biliary stenting	Pancreaticoduodenectomy, distal pancreatectomy, splenectomy	Percutaneous transhepatic catheter, biliary stenting
	Liver, bile duct	Endoscopy, biliary stenting	Hepatectomy, liver transplant	Percutaneous transhepatic catheter
	Colon, rectum	Endoscopy	Colectomy, ostomy creation, abdominal peritoneal resection	Diverting ostomy, stent
Pelvis				
	Ovary	Diagnostic laparoscopy, peritoneal washings	Bilateral salpingo-oophorectomy, hysterectomy	Debunking, ostomy creating, paracentesis

Table 7.1 (continued)

Body	Location	Diagnostic/adjuvant	Definitive	Palliative
	Uterus	Endometrial biopsy	Bilateral salpingo-oophorectomy, hysterectomy	
	Prostate	Transrectal ultrasound and biopsy	Prostatectomy	Transurethral resection of prostate, orchiectomy
Extremities				
	Arms and legs	Incisional biopsy	Wide local excision, amputation	Amputation

The extent of a patient's disease (stage of cancer) plays a crucial role in decision-making in oncologic surgery. Stage can be thought of generally as localized, regionally invasive, and metastatic. Formal staging systems exist for each cancer and can help guide treatment options and predict patient survival, recurrence, and overall outcomes. Generally, the major goal of oncologic surgery is removal of all tumor tissue, referred to as obtaining a negative margin. This means that all cancerous tissue is removed with a surrounding rim of normal tissue; the final determination of this depends on pathologic evaluation of the surgical specimen. Surgery is thought to be potentially curative if a negative margin can be obtained. Obtaining a negative margin is usually only possible in tumors that remain localized or regional. With few exceptions, patients with cancers that have metastasized from the primary tumor to distant sites (usually through the blood) are rarely candidates for a definitive surgery with curative intent. However, surgical procedures may be required in these patients for diagnostic or staging purposes – to determine if there is distant spread. Also, a wide range of palliative surgical procedures can be performed in cancer patients, even many with advanced-stage cancers.

Once the surgeon has met with the patient and determined the surgical treatment plan (taking into account tumor and patient factors and discussing risks/benefits of surgery), an operation can be performed. Based on the intent of surgery, oncologic operations can be divided into three major categories: diagnostic/adjuvant procedures, definitive treatment, and palliative procedures.

Diagnostic/Adjuvant Procedures

With many types of cancers, a staging procedure is essential to determine if there has been any spread of the cancer beyond its primary location. A staging procedure determines if a patient is a candidate for a definitive surgery by obtaining tissue, most often lymph nodes, for pathologic review. Often, these diagnostic procedures

are minimally invasive and are performed by percutaneous, endoscopic, or image-guided biopsy. In the case of some intra-abdominal cancers, laparoscopy (filling the belly with gas and examining the organs with minimally invasive video-assisted equipment via small (keyhole) incision) is used for direct visualization to examine for intra-abdominal or peritoneal metastasis. Similarly, for some chest and lung cancers, thoracoscopy (similar to laparoscopy, but looking into the chest) can be done to assess the extent of cancer and the potential resectability of the tumor. Also for chest cancers, mediastinoscopy, a video-assisted device, can be passed through an incision in the neck into the chest behind the sternum to obtain lymph nodes that are positioned near the trachea.

Adjuvant procedures are offered to patients with a cancer diagnosis to facilitate treatment (i.e., obtain vascular access, place feeding tubes). Infusion ports, which offer durable, subcutaneous vascular access for infusion of chemotherapy agents or intravenous fluids, are frequently required to receive chemotherapy or immunotherapy. Patients with head, neck, and esophageal cancers may experience compressive symptoms such as progressive dysphagia to solids and liquids and become unable to keep up nutritional requirements during neoadjuvant treatment and may require placement of feeding access via a gastrostomy (feeding tube into the stomach through abdominal wall) or jejunostomy (feeding tube into the jejunum/small bowel through abdominal wall).

While many of these diagnostic or adjuvant procedures require general anesthesia and endotracheal intubation, they are quick (typically less than 1 hour), result in minimal patient discomfort, rarely require extended use of pain medication, and almost always allow patients to go home after the procedure without admission to the hospital. Because they are not designed to cure the patient, diagnostic and adjuvant procedures are more minimally invasive, are better tolerated, and result in a risk/benefit ratio favoring the patient. But even these minor surgical interventions can have major risks postsurgery, especially in frail, older, debilitated cancer patients. Moreover, these procedures are often closely followed by aggressive treatments, such as chemotherapy, radiation, or further definitive surgical treatment, and can start a marked and rapid deconditioning of already frail patients.

Definitive Treatment

Patients who undergo definitive surgical treatment for their cancer do so with the intent of complete resection of the cancer, usually with intent to cure. Depending on the type of cancer and the size, definitive cancer operations resect a portion or the entirety of the organ from which they arise. For example, a small thyroid cancer localized to one side of the thyroid can be treated with hemithyroidectomy, meaning half the thyroid is surgically removed and the opposite side of the thyroid is left in place. However, larger tumors require a total thyroidectomy. The general principle of definitive oncologic surgical treatment is that the larger or more aggressive/extensive the tumor, the more extensive the operation required for removal.

The principle of oncologic surgery is to approach the area of cancer with an incision that allows access to the entire planned area of resection. In most circumstances, if all cancer is not removed during the surgery (without negative margins), there is no benefit to the patient undergoing surgery. An exception is some cancers in which debulking surgeries – removing as much of the cancer as possible, but not achieving a negative margin – can still be beneficial (neuroendocrine tumors, ovarian cancer). In some cancer operations, like breast cancer surgery, positive margins require an additional surgery to re-excise the cancer left behind. During surgery, care must be taken to avoid important surrounding structures, such as nerves, blood vessels, and uninvolved surrounding organs. This requires a surgical oncologist to know all aspects of anatomy in the operative area, as well as to be familiar with the specifics of the patient's anatomy with preoperative imaging. Cancer surgery is a balancing act between taking enough tissue to completely excise the cancer cells, but leaving behind vital structures that the patient needs to survive and function.

An important distinction between types of definitive cancer surgeries performed for both the thorax and abdomen is the standard open procedure with a large incision that all surgical work is performed through, versus video-assisted or laparoscopic/laparoscopic-assisted procedures where multiple small incisions are used. The decision to perform a minimally invasive or open surgery depends on the location and size of the tumor as well as surgeon experience.

The physiologic effects of a thoracotomy (an open incision in the chest) versus a video-assisted thoracoscopic surgery (VATS) have distinct effects on a patient recovery (Fig. 7.1). Patients undergoing VATS have been shown to return to baseline function

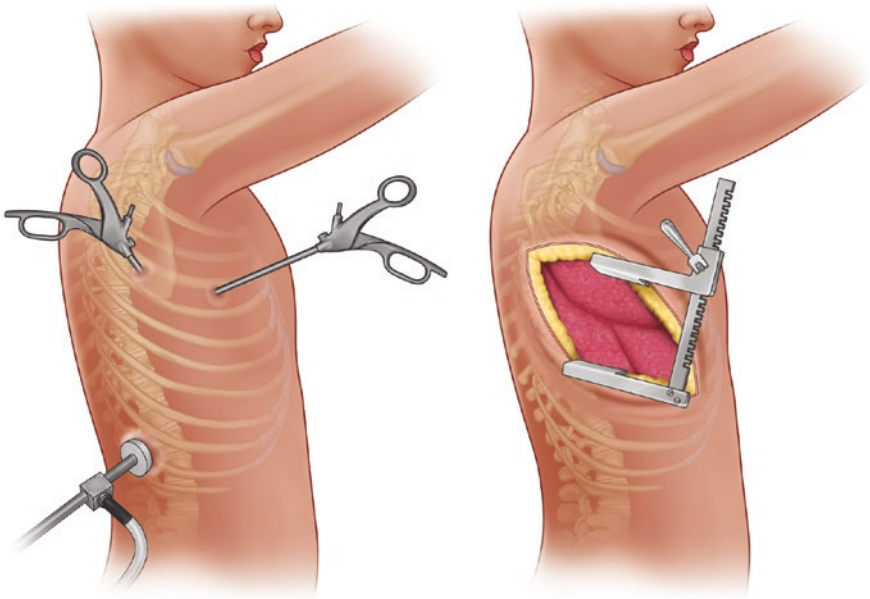

Fig. 7.1 Thoracoscopy incisions (*left*), posterolateral thoracotomy incision (*right*)

after 2 months, compared to open thoracotomy patients taking 3 months or more [1]. For cancers located in the abdomen and pelvis, an exploratory laparotomy incision is a long incision through all layers of the abdominal wall (placed on the abdominal wall to maximize access to the operative anatomy) allowing access to the entire intra-abdominal and pelvic cavities. Laparoscopic abdominal surgery involves multiple 5–11 mm incisions placed through the abdominal wall allowing the abdomen to be insufflated with air and a camera and laparoscopic instruments to be inserted into the abdomen (Fig. 7.2). Open surgery has been shown to have longer hospital stays, more pain, and more difficulty returning to baseline physiologic function. Unfortunately, cancer operations more often require open procedures over benign procedures, given the nature of cancer surgeries and the factors of tumor location, tumor size, and involvement of surrounding structures. The need for large, morbid procedures in patients that are already deconditioned from both disease and adjuvant treatment puts patients undergoing definitive cancer surgery at a high risk of accelerated loss of physical function.

Palliative Procedures

The goal of palliative surgical procedures is to improve the quality of life of patients with a cancer diagnosis. The procedures are meant to decrease pain and treat symptoms. The goal of these surgical procedures is not to remove all cancer, but to address an anatomic consequence of the cancer that is causing symptoms.

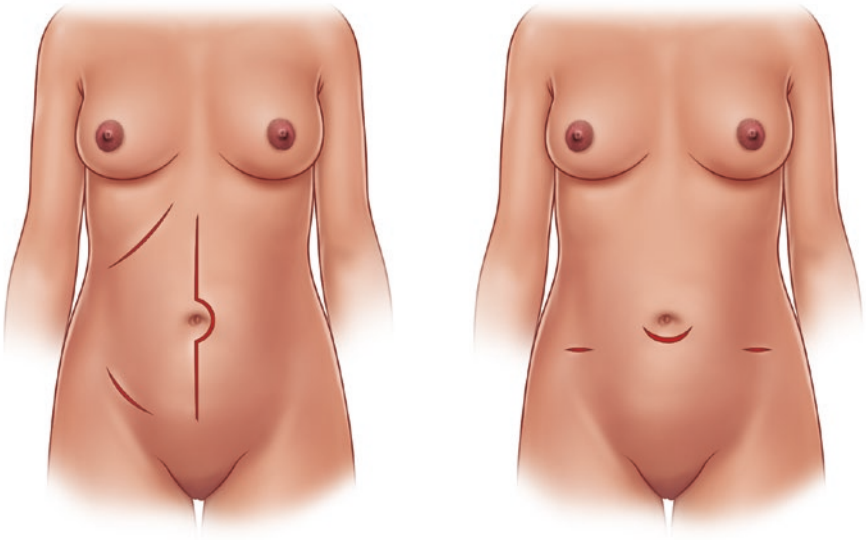

Fig. 7.2 Right upper quadrant (Kosher) incision, right lower quadrant (McBurney) incision, and midline laparotomy incision (*left*), abdominal laparoscopy incisions (*right*)

A common symptom of advanced cancer is pain. While pain secondary to cancer is typically addressed with pain medication, in some cases, surgical interventions are necessary to address refractory pain. Some examples include breast lesions that are invading chest wall, causing skin irritation and require surgical debridement, or extremity lesions such as sarcomas requiring an amputation for pain control. In the case of advanced pancreatic cancer, a celiac plexus block or neurolysis may be offered in rare cases. This involves accessing the nerves associated with the pancreas either via a needle under imaging guidance or with video-assisted techniques, and disrupting the nerves transmitting the pain from the pancreas with caustic chemicals, leading to a decrease in pain.

A common problem of advanced intra-abdominal cancers is bowel obstructions. Because of mass effect or adhesion of the bowel secondary to tumor, the contents of the intestines are unable to pass through the digestive tract. This causes backup of the bowel contents, resulting in bloating, abdominal pain, nausea, vomiting, and potentially a bowel perforation. Depending on the area of the obstruction, surgery can be done either to bypass the area of obstruction and create an ostomy (divided bowel that is brought to the abdominal wall to allow emptying of stool into a stoma bag) or place a gastrostomy tube to allow venting of backed up material and gas resulting in resolution of symptoms.

As a whole, palliative surgeries vary widely, but the underlying principle is that the purpose of the surgical intervention is symptom control and not curative treatment. Because of this, the most minimally invasive techniques possible are used in order to avoid symptoms of pain and deconditioning.

Common Symptoms After Surgery

The symptoms that patients most commonly experience after oncologic surgery vary depending on the location of the surgery and by the invasiveness of the procedure (size of incision, the amount of tissue removed, organ(s) resected, and irritation and damage to surrounding tissues). Because symptoms are most severe after definitive surgeries performed for oncologic reasons, we will focus on symptoms experienced by patients after definitive cancer surgeries.

General

General side effects after a major surgery include fatigue, deconditioning, nausea, anorexia, systemic inflammation, sleep disturbances, and most commonly, pain [2]. Definitive cancer surgeries are usually extensive, long surgeries that require general anesthesia and are physically demanding. Many of the immediate side effects are secondary to extended anesthesia required to perform the surgery. These include postoperative nausea, anorexia, and fatigue. Sleep disturbances and fatigue can be persistent for several weeks after surgery. The combination of a reaction to the body

processing anesthesia, cytokines, and stress hormones from the physiologic challenges of surgery are likely responsible for each individual's reaction to surgery and the general side effects they experience [3].

Pain is a common symptom after any oncologic surgery. This is a consequence of surgical incision through skin, subcutaneous tissue, muscle, and fascia. Additionally, disruption of nerves surrounding and associated with cancerous tissue can also be associated with surgical pain. Pain can vary dramatically per individual and is difficult to quantify; it is measured via patient reporting typically through a visual analog scale. After surgery, pain control is often a major limiting factor that prevents patients from ambulating, returning to baseline activities of daily living (ADLs), and being discharged from the hospital. However, treatment of pain, particularly through narcotic pain medications, can contribute to a prolonged recovery because of side effects from medications.

Head and Neck

Head and neck cancers encompass many different organs including the oral cavity, nasal cavity, larynx, pharynx, and salivary glands. These are often aggressive cancers treated with multimodality chemotherapy, radiation, and surgery. The head and neck have a dense supply of nerves and tissue that is important for many functions associated with this anatomical area. Surgeries in the neck can result in symptoms of dysphagia or odynophagia (difficulty and painful swallowing), leading to difficulty with maintaining nutrition. Occasionally, surgeries of the pharynx and larynx can result in difficulty or inability to speak. Removal or dysfunction of the salivary glands after cancer surgery can result in dry mouth, numbness of the face, and facial nerve dysfunction or paralysis [4].

Disfigurement and the psychosocial symptoms of a cancer operation in such a visible area are particularly of concern to individuals with head and neck cancer. Since scarring and tissue loss cannot be hidden by clothing or bandages, patients can experience symptoms of depression or isolation [4].

Brain

Symptoms after surgery for brain cancers can vary depending on areas of the brain that are affected by the anatomic position of the tumor. Common symptoms include sensorimotor deficit resulting in loss of function of upper or lower extremities, aphasia, ataxia, dysphagia, and visual-perceptual deficits [5]. All of these symptoms can significantly affect a patient's quality of life and ability to return of baseline after neurosurgery.

An additional common symptom after neurosurgery, specifically craniotomy, is a post-craniotomy headache. This has been found to be present in up to 100% of patients in some studies, and up to 30% of patients report symptoms for up to 6 months postoperatively. These headaches are reported to cause significant interference with activities of daily living, especially with postoperative movement [6].

Breast/Soft Tissue

Surgery for breast cancer typically results in symptoms associated with musculoskeletal dysfunction. Depending on the extent of the cancer operation, breast tissue and lymph node tissue closely associated with muscles and nerves of the chest wall and axilla can be affected (Fig. 7.3). Patients will often have significantly decreased range of motion of the upper extremities. Additionally, depending on the extent of lymph node removal, patients can experience a disruption in the lymph flow from their distal arms back to their axilla over the long term. This can result in lymphedema, or swelling secondary to accumulation of lymphatic fluid in their arm, leading to decreased range of motion and a feeling of heaviness of the upper extremity that can sometimes compromise ability to complete ADLs [7]. Chronic lymphedema can lead to the development of lymphangiosarcoma, a sarcoma of the lymphatic tissue, which may result in extremity pain, swelling, amputation, and possibly death [8].

Extremity

Extremity surgeries for cancer most often are due to sarcomas. Sarcomas are tumors that arise from connective tissue such as bone, fat, cartilage, and muscle. Sarcomas are a rare subset of cancer that can occur anywhere in the body, although 50% of sarcomas are located in the extremities. Historically, the treatment of extremity sarcoma was an amputation of the affected limb; however, presently many of these tumors can be treated with limb-sparing surgeries with equal oncologic outcome

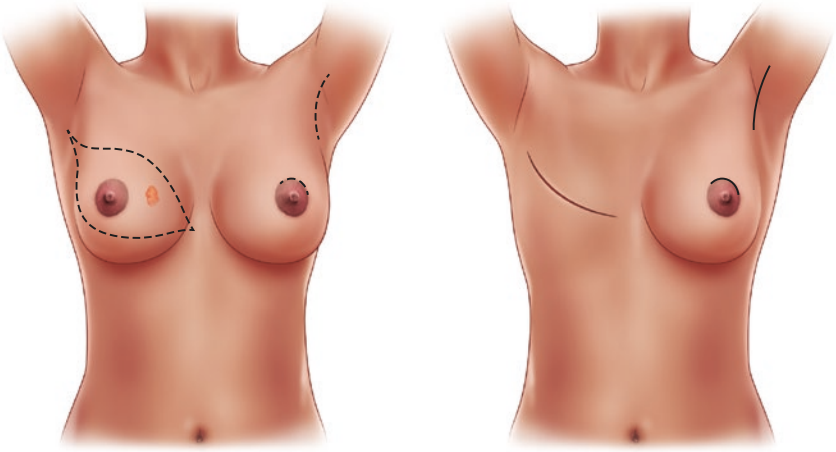

Fig. 7.3 Planned right breast mastectomy incision and left breast periareolar and axillary incisions (*left*), same incisions after closure (*right*)

[9]. Both amputation and limb-sparing surgery carry the morbidity of mobility dysfunction. As expected, patients undergoing amputation can be candidates for a prosthetic limb, which can help overall with the ability to ambulate and perform ADLs. Even limb-sparing surgeries have some degree of loss of function of the affected limb and also require intense rehabilitation and strategies to restore or cope with functional loss [10].

Lung

Thoracic surgeries for lung cancer are very common and are considered the standard of care for most early lung cancers. Given improved screening and increase in laparoscopic techniques, outcomes for lung cancer surgery have improved dramatically over time. In addition to the general side effects of all surgical interventions (pain, fatigue, nausea, etc.), lung surgery also causes significant dyspnea or shortness of breath [11]. Loss of functional lung is reported to cause significant dyspnea with exertion and is the most common postoperative limitation after thoracotomy for lung cancer [12].

In addition to expected acute postoperative pain, thoracotomies can result in long-term chronic pain. Rates of significant chronic pain vary dramatically in the literature, anywhere from 20% to 80% depending on the definition of chronic pain [13–15]. Using the definition of "persistent continuously or intermittently for more than 3 months after surgery and different from preoperative pain," Mongardon et al. found the rate of chronic pain to be 48% and associated with younger age and less severe American Society of Anesthesiologists (ASA) score [16]. This unique issue of chronic post-thoracotomy pain can lead to limitations in younger and healthier patients, who would typically be expected to recover faster than their older and sicker counterparts.

Abdomen

A wide variety of symptoms can result from abdominal surgery for a cancer operation. Commonly, any surgery that involves resection of the small or large bowel can result in significant change in bowel habits for patients that may or may not remain permanently. If large portions of the bowel are resected, the absorptive capacity may be decreased to the point where patient experience chronic diarrhea. Surgeries on the upper gastrointestinal (GI) tract, particularly the stomach, may result in early satiety and chronic nausea and emesis. Surgeries for pancreatic cancer may result in a loss of important digestive enzymes, and if a critical portion of the pancreas is resected, patients may experience persistent hyperglycemia and develop diabetes. Oncologic surgeries of the GI tract can cause significant dysfunction for oral intake, putting patients at risk for malnutrition and weight loss [17].

Pelvis

Symptoms associated with surgeries of the pelvis revolve around complete removal of organs during cancer operations. For example, gynecological malignancies such as endometrial and ovarian cancers often require removal of the ovaries, uterus, and fallopian tubes. This leads to symptoms similar to menopause including hot flashes, osteoporosis, vaginal dryness, as well as loss of fertility [18]. Surgeries for prostate cancer can similarly result in sexual dysfunction given the close proximity of nerves to the prostate [19]. Additionally, for both men and women, cancer operations in the pelvis can result in urinary incontinence from both neurological damage and anatomic changes in the muscles of the pelvic floor [20–21].

Benefits of Exercise During Surgical Recovery

A recent shift in clinical care has highlighted the importance of Enhanced Recovery after Surgery (ERAS) paradigms. ERAS is an evidence-based care improvement process for surgical patients initially established in 2001 that has now become standard of care; it involves preoperative, intraoperative, and postoperative recommendations [22]. ERAS protocols aim to reduce cost, shorten length of stay, and decrease morbidity and mortality after surgery. As part of the postoperative recommendations, ERAS protocols now include early mobilization within 24 hours following surgery, with the goal of ambulation during that time. Multiple review articles have found that surgical patients who underwent an early rehabilitation program have improved pulmonary function (measured with forced vital capacity), improved fatigue, increased functional mobility, and decreased length of stay when compared with usual care patients [23–24]. Exercise should also be a mainstay of the postoperative management of oncologic patients. Cancer patients experience improved functional capacity, decreased fatigue, reduced pain, shortened hospital stays, improved mood, enhanced immune function, and improved psychosocial outcomes with postoperative exercise [25]. While this is a new area for research, the literature continues to grow as researchers and clinicians examine the effect of exercise during surgical recovery in specific cancers. We present a review of the current literature that exists within different cancer subtypes.

Breast Cancer

There has been considerable debate in the literature about the benefits of early postoperative exercise in the breast cancer population, given the concern for increased wound drainage, delayed wound healing, and risk for long-term lymphedema. A Cochrane review found significantly improved shoulder flexion and abduction range

of motion when structured exercise was initiated early within 1 week of surgery, compared to delayed initiation [26]. Early postoperative physical therapy (PT) yields additional benefits in shoulder range of motion and shoulder function. These findings were replicated in a more recent abstract published as part of the Lymphedema Education and Prevention study; surgical patients who underwent an exercise and PT program had significantly greater shoulder range of motion in both arms at 12 months post-op, compared to those who did not receive the exercise intervention [27].

While randomized controlled trials have demonstrated that progressive resistive exercise not only is safe in breast cancer survivors, but also reduces the risk of lymphedema, there are fewer data on the effects of exercise in the early postoperative period [28–29]. Lymphedema may be prevented with early post-op exercise; Torres Lacomba et al. observed that in patients status post breast surgery with axillary lymph node dissection who underwent early PT with manual lymph drainage (within 1 month post-op), there was a reduced risk of secondary lymphedema (lymph fluid in the interstitial space) within 1 year, compared to those who did not have early PT [30].

Lung Cancer

Traditionally, lung cancer patients limit physical activity to avoid the so-called dyspnea spiral; patients develop breathlessness and then avoid additional activity because of their symptoms, which results in functional disability [31]. This cycle is only exacerbated following lung surgery. Perioperative pulmonary rehabilitation has been shown to improve exercise tolerance, dyspnea, and quality of life in lung cancer patients following lung volume reduction surgery [32]. As formal pulmonary rehabilitation programs remain underutilized, alternate exercise programs offer another approach to target and improve symptoms. A recent Cochrane review updated the evidence on exercise within 12 months following lung surgery in non-small cell lung cancer (NSCLC) [33]. This review included eight studies that investigated the effects of combination aerobic and strengthening training over periods from 4–20 weeks. They found evidence of improved quality of life, improved exercise tolerance and fitness level (measured with 6-minute walk test and a cycling test), improved lower extremity strength, and decreased breathlessness in these patients. A separate study also found that in patients who initiated a daily walking program within 1 week of lobectomy, they measured improved forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) at 3 months post-op [34].

Gastrointestinal Cancer

Patients who undergo abdominal surgery have an increased risk of postoperative ileus and constipation. Early ambulation following abdominal surgery in the non-oncologic population has been shown to decrease time to defecation, and similar findings have been described in the colon cancer population status post colectomy [35–36].

In colorectal cancer (CRC), patients experience a functional decline following surgery and some are unable to recover their preoperative functional status [37]. Van Zutphen et al. observed that in newly diagnosed CRC patients who underwent tumor resection, those who increased their physical activity level to >150 minutes per week (compared to <150 minutes preoperatively) were more likely to recover their physical functioning by 6 months post-op [38]. To our knowledge, this has been one of the only studies to examine exercise at 1 year post-op. However, other studies have shown that a short-term exercise program in CRC survivors status post resection significantly improves aerobic fitness levels (measured via treadmill test), peak oxygen uptake, and upper and lower body strength [39–40]. Epidemiologic studies have also shown post-diagnosis physical activity is associated with an overall decrease in CRC mortality [41].

Similar to colorectal cancer, there is a lack of data within the postsurgical gastric cancer population. One recent small open pilot study by Cho et al. examined the effects of a 10-week exercise program starting in the hospital within 1 week of laparoscopic or robotic gastrectomy [42]. The exercise program began with early ambulation and range-of-motion exercises and progressed to a resistance program by 2 weeks post-op. There were no adverse events, and at the completion of the study, the patients had significantly improved endurance, global health status, and emotional functioning when compared to their preoperative baseline.

Neurological Cancer

Patients who undergo surgery for primary neurological cancers (glioblastoma, meningioma, astrocytomas, etc.) can experience motor deficits (weakness, ataxia, spasticity) as well as communication, cognitive, and functional deficits; these deficits may be secondary to their tumor or a result of the surgery [43–44]. This population is somewhat unique as they may be able to participate in an inpatient acute rehabilitation course following surgery; their diagnoses are covered by two rehabilitation impairment codes: non-traumatic brain dysfunction and non-traumatic spinal cord dysfunction. Acute inpatient rehabilitation in the United States consists of 3 hours of physical therapy, occupational therapy, and/or speech therapy 5 days per week. To our knowledge, there are no formal studies that evaluate a postoperative exercise program for neuro-oncologic patients; however, observational studies have shown that early postoperative brain tumor patients experience improved balance, posture, and functional independence measure (FIM) scores following an acute rehab course [45–46].

Gynecologic Cancer

There is a paucity of data surrounding postoperative exercise in the gynecologic cancer population. A small study was published in 2015 supporting the feasibility

of a postoperative weekly exercise program starting 6 weeks after surgery in endometrial cancer patients; however, it is unclear if this led to the design of a larger, randomized controlled trial [47].

Prostate Cancer

Given that prostate cancer patients mostly commonly experience urinary symptoms following surgery, physicians traditionally have prescribed Kegel (pelvic floor) exercises postoperatively, and rarely include other types of exercise training [48]. A small, randomized study examined the effects of a combined exercise program (resistance, flexibility, and Kegel exercises) in twice weekly sessions starting postoperative week three after laparoscopic radical prostatectomy, compared to Kegel exercises alone [49]. The patients who underwent the combined program had significantly improved functional physical fitness, balance, and urinary incontinence compared to the control group. A more long-term study by Zopf et al. initiated a weekly exercise program starting 12–18 weeks after radical prostatectomy for 15 months, compared to the control group (no intervention) [50]. At the study conclusion, the exercise group experienced significantly improved physical fitness and global functioning, and significantly decreased treatment-related side effects (dyspnea, urinary incontinence).

Head and Neck Cancer

Similar to breast cancer, head and neck cancer patients also frequently experience shoulder morbidity, chronic neck pain, and a higher risk of secondary lymphedema, related to a radical neck dissection. In patients with early postoperative edema (up to postoperative day 30) following resection with neck dissection, manual lymphatic drainage twice weekly and compression garments significantly reduced edema after 6 weeks [51]. A small feasibility study demonstrated significantly improved shoulder pain and external rotation in patients who underwent postoperative progressive resistance exercise training compared to patients undergoing usual care [52]. Shoulder pain in this patient population was re-examined in a Cochrane review, which found limited evidence supporting postoperative progressive resistance training over standard physical therapy; however, more data is needed on this topic [53].

Bone Cancer

While these types of cancer are more prevalent in the pediatric population, they may present in an adult patient. Similar to patients with neurological cancers, patients with bone cancer may be eligible for acute rehabilitation following amputation of an extremity.

Adverse Effects of Postoperative Exercise

There is a paucity of data examining formal exercise programs in both the non-oncologic and oncologic surgical patient populations. Upon review of the literature detailed above examining postoperative exercise in oncologic patients, there were no serious adverse effects reported. In the surgical literature, the evidence supports postoperative fast-track programs and ERAS protocols in both non-oncologic and oncologic populations, which typically include early extubation and ambulation by postoperative day one [54]. In studies examining ERAS protocol in colorectal cancer patients' status post-resection, postoperative adverse events such as anastomotic leaks, incision infection, and cardiorespiratory insufficiency occurred at lower or equal frequencies in patients receiving early mobilization (5–22% in the mobilization arms versus 21–45% in the control arms) [36, 55–56]. However, in patients undergoing exercise in the immediate postoperative period, there is a risk of increased wound drainage from the surgical incision, specifically noted in the breast cancer population [26]. Clinicians supervising exercise in the immediate postoperative period should be especially conscious of surgical drains, vacuum-assisted wound closure, and/or ostomies during activity.

Special Considerations

As per American College of Sports Medicine (ACSM) guidelines, patients with ostomies can safely participate in ambulation; however, they should avoid contact or water sports [57]. They can progress to include supervised resistance exercise; however, they should avoid excessive intra-abdominal pressure and should establish consistent infection prevention practices prior to initiating a structured exercise program. In patients who perform strenuous exercise too early following abdominal surgery, there is a risk of an abdominal wall hernia. Fracture risk should be assessed prior to starting a fitness program in patients with bony metastases, osteoporosis, or on hormonal therapy. These populations may require activity modifications to avoid fractures.

Guidelines for Postoperative Exercise

The following are expert advice statements on postoperative exercise in oncologic patients created in the absence of published evidence. These are a product of the authors' clinical experience, as well as the above review of the literature and the ACSM guidelines for exercise in cancer survivors [57]. The above review highlights the need for more peer-reviewed literature on both the efficacy and safety of formalized exercise programs in the immediate and delayed postoperative periods in various cancer conditions.

Prior to starting any postoperative exercise, it is important to clarify any precautions (especially weight bearing and range of motion) with the surgeon. If there are no contraindications, we recommend that all oncologic patients should aim for early mobilization by postoperative day one. If patients are eligible for and able to receive inpatient physical and/or occupational therapy, this allows for supervised ambulation and range of motion.

From postoperative days 0–14, patients are able to safely perform ambulation, flexibility, and range-of-motion exercises. By postoperative day 14, the proliferative phase of wound healing is winding down and the remodeling phase has begun to recover the normal tissue structure [58]. At this point, consider adding 30–60 minutes of supervised aerobic and progressive resistance training to the patient's exercise program once medical clearance is obtained from the surgeon. We recommend evaluation by a physician with a strong background in both musculoskeletal anatomy and clinical practice (i.e., sports medicine, physiatry, etc.) before beginning a structured exercise program. All exercise should be individualized to the patient's exercise level and symptom-limited.

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Chapter 8
During Infusion Therapy

Kristin L. Campbell and Amy A. Kirkham

What Is Infusion Therapy?

Infusion therapy involves the administration of medication through a needle or catheter. In the context of cancer, infusion is a common delivery method for chemotherapy. Chemotherapy, which can also be delivered orally, is a main stay of cancer treatment, along with surgery and radiotherapy. Immunotherapy is a recent advancement in cancer therapy that helps the immune system to fight cancer. Infusion is one method of administering immunotherapy. At this point immunotherapy is used less widely than surgery, radiation, and chemotherapy in cancer treatment, but may soon be a mainstay for several cancers [1]. The administration of immunotherapy varies by the type of cancer, stage of cancer, type of immunotherapy approach being used, and how each individual responds to the treatment. This chapter will focus primarily on the role of exercise concurrent with chemotherapy, as the role of exercise in the context immunotherapy is a new area where little is known at this time.

Chemotherapy involves the use of powerful drugs to kill rapidly dividing cells in the body or slow down their rate of growth. There are many classes of chemotherapy drugs, and each target the cancer cells in different ways with a primary aim to interrupt the cancer cell cycle and thereby growth of the tumor. The drugs are commonly used in combinations in order to maximize the ways the cell cycle of the cancer cell can be interrupted to slow or prevent growth. For early-stage or locally advanced cancers, chemotherapy is used either with curative intent to either shrink tumors before surgery (known as neoadjuvant chemotherapy) or with the aim to eliminate remaining

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microscopic cancer cells after surgical removal of the tumor (adjuvant chemotherapy). With advanced cancer where the cancer has spread to other areas of the body distant from the primary tumor, known as metastasis, chemotherapy is used to slow down or stabilize the growth of the primary tumor and metastatic growths, but does not have a curative intent. Chemotherapy can also be used to relieve symptoms that result from where the tumor is located, for example, pain or pressure on the spinal cord.

Chemotherapy infusions are commonly given in cycles, which mean the length of time between each treatment infusion. Typically a chemotherapy infusion is administered over several hours, usually in a cancer center or other healthcare facility. Then, the individual returns 1–3 weeks later for the next infusion. This is repeated for several cycles, with 4–8 cycles, for a total of 9–24 total weeks being the most common length to neoadjuvant or adjuvant chemotherapy for individuals with early-stage cancer. This treatment approach using cycles of chemotherapy is used because chemotherapy targets not only cancer cells but also other fast-dividing healthy cells, such as the hemopoietic cells in bone marrow that produce new red and white blood cells and the epithelial cells lining the mouth or digestive system. The body needs time to recover from the negative effects on healthy cells in between cycles before receiving the next chemotherapy dose. The schedule of chemotherapy is based on delivering the maximally effective dose to the tumor while allowing the individual to tolerate the side effects. This approach to treatment has implications for prescribing exercise during chemotherapy.

Common Side Effects of Infusion Therapy

There are some general side effects in common for most chemotherapy regimens, as well as specific side effects related to particular chemotherapy drugs being used (Table 8.1). The common *acute* side effects of chemotherapy are primarily related to the effect of the drugs on quickly dividing cells in the body. These include nausea and diarrhea (as quickly dividing cells line the gastrointestinal tract), reduced immune function (due to impact on white blood cell production in bone marrow),

Table 8.1 Common side effects of chemotherapy that influence exercise tolerance

Timing		
Acute[A]	Long-term[B]	Late[C]
Fatigue Nausea/vomiting Hair loss Peripheral neuropathy Altered executive cognitive function	Fatigue Weakness Neurotoxicities Weight gain or weight loss**	Cardiovascular disease Frailty Second cancers

[A] Onsets mainly during treatment and resolves when treatment is complete
[B] Onsets during or shortly after treatment and does not resolve after completion of treatment
[C] Onsets many months or years after completion of treatment
**The direction of weight changes during chemotherapy are dependent upon the cancer type, but weight gain usually leads to a disproportionate increase in body fat while weight loss usually leads to a disproportionate loss of muscle.

and fatigue (which has a multifactorial origin but due in part to anemia from a reduction in red blood cell and hemoglobin production), along with hair loss and nail changes (as hair follicles and nail cells are also quickly dividing cells). Some of these effects can resolve soon after the completion of chemotherapy (i.e., return of hair growth), while some side effects can persist after treatment is completed and take longer to resolve (i.e., cancer-related fatigue or deconditioning). There are also side effects known as "*late*" effects, which were not necessarily evident at the time of treatment but can manifest months or years later. One example is cardiovascular disease. Cardiovascular disease has recently been recognized as an important competing risk of death for individuals diagnosed with numerous cancer types with lower cancer mortality rates (e.g., breast, prostate, testicular, sarcoma) [2–4]. While the development of cardiovascular disease and related mortality is multifactorial and likely consists of the compounding of numerous risk factors in balance with numerous protective factors, the cardiovascular side effects of cancer therapies are considered one of the major risks [5]. Of interest, improving or at least maintaining healthy lifestyle behaviors, especially physical activity during the active cancer treatment period, can play a role in protection from this late side effect [5].

An example of a *specific* side effect of a chemotherapy drug is chemotherapy-induced peripheral neuropathy, which is a specific side effect of several drugs, including oxaliplatin which is commonly used in treatment for colorectal cancer, and taxanes, paclitaxel and docetaxel, which are commonly used to treat breast cancer. This side effect presents as tingling, numbness, pain, or altered sensitivity, commonly in the hands and feet. Cardiotoxicity, or injury to the heart muscle, is a specific side effect of a family of chemotherapy agents called anthracyclines, which include doxorubicin, epirubicin, idarubicin, and daunorubicin. This side effect is often asymptomatic, especially in the early stages of development, and by the time it becomes symptomatic, irreversible damage to the heart muscle may have occurred. Cardiotoxicity is diagnosed in the oncology setting by a reduction in the ability of the heart to eject blood (ejection fraction), which can only be measured by cardiac imaging tests such as echocardiogram, multi-gated acquisition (MUGA) scan, or cardiac magnetic resonance imaging scan, which is the gold standard test. Some cancer treatment centers may also monitor for early signs of cardiotoxicity using blood tests for specific markers that are released from the heart muscle in response to injury from chemotherapy. Chemotherapy can also commonly cause other cardiovascular side effects including resting tachycardia and hypotension [6]. While the relationship of these side effects with cardiotoxicity is not known, both conditions could result in patient symptoms including dizziness, lightheadedness, difficulty in changing body position, feelings of high heart rate, as well as a potential need for hypertension medication dose adjustments. Exercise professionals working with individuals receiving chemotherapy should be aware of the prevalence of tachycardia and hypotension, regularly monitor for them, and adjust exercise plans as necessary [6].

From the start to end of chemotherapy, the pattern of how the side effects present differs between individuals. A steroid is often prescribed as an anti-emetic for the first 3–5 days of a chemotherapy cycle, which can delay the peak impact of treatment symptoms until after the patient stops taking the steroid. Generally, the acute side effects (i.e., nausea, fatigue, immune compromise) peak in the 3–7 days

following the infusion and then start to resolve prior to the next infusion. However, due to the cumulative nature of chemotherapy side effects, patients will not likely return to their pretreatment physical well-being. For specific side effects, such as peripheral neuropathy, these tend to accumulate with each treatment cycle and then there is a slow resolution in most cases once the treatment is stopped.

For immunotherapy, the side effects depend on the type of immunotherapy, dose, and how it is administered (i.e., by infusion or orally). A common side effect is flu-like symptoms, such as fever, chills, muscle aches, and nausea, which can be immediate and decrease with subsequent treatments as the body gets used to the particular immunotherapy being used. Fatigue and skin rashes are also common side effects [7].

Role of Exercise during Infusion Therapy

Exercise has been shown to improve several of the common side effects of chemotherapy, as well as help individuals to maintain their physical function and quality of life during treatment. The 2019 American College of Sports Medicine (ACSM) Roundtable Guidelines on Exercise for Cancer Survivors reported that specific doses of aerobic, combined aerobic plus resistance training, and/or resistance training could improve anxiety, depressive symptoms, fatigue, physical functioning, and health-related quality of life (Table 8.2) [8]. There is also emerging evidence that exercise may improve sleep disturbances during and after treatment, but more high-quality research was needed to confirm this. Implications for other side effects of chemotherapy, such as cardiotoxicity, chemotherapy induced peripheral neuropathy, cognitive function, and nausea remain uncertain [8]. However, it is important to note that the majority of available research is still in individuals with the most common cancer types, namely early-stage breast cancer and prostate cancers. Differences among cancer survivors by cancer type are known to exist (i.e., demographics, cancer stage, prognosis, treatments received, and associated side effects). At this time it is reasonable to extrapolate the benefits of exercise to cancer survivors of other cancer types with the use of clinical judgment by the exercise professional in prescribing and monitoring exercise, as well as being aware of the types of treatment being received and anticipated side effects.

Table 8.2 Expected patient benefits from exercise training in early-stage cancer survivors by mode from 2019 ACSM expert consensus statement on exercise guidelines for cancer survivors [8]

Aerobic	Resistance	Aerobic plus resistance
Reduced anxiety	Less fatigue	Reduced anxiety
Fewer depressive symptoms	Better quality of life	Fewer depressive symptoms
Less fatigue	No risk of exacerbating lymphedema	Less fatigue
Better quality of life	Improved perceived physical function	Better quality of life
Improved perceived physical function		Improved perceived physical function

There is little known about the role of exercise concurrent to immunotherapy. A small feasibility pilot study by Lacey et al. [9] demonstrated that integrating an individualize exercise program, developed by an Accredited Exercise Physiologist, as part of a holistic supportive care program, was feasible for individuals with metastatic melanoma being treated with pembrolizumab. Much more research is needed to better understand the role of exercise for individuals receiving immunotherapy.

The goal of prescribing exercise in any context is commonly to improve an individual's components of physical fitness, including cardiorespiratory fitness (i.e., VO_2peak), muscular strength and endurance, body composition, and flexibility. However, a reduction in *cardiorespiratory fitness* during chemotherapy is well documented, as measured by VO_2 peak or 6-minute walk test [10]. Typically there is a reduction in usual physical activity, including leisure time, occupation, and household settings, related to a cancer diagnosis (i.e., anxiety, worry, lack of time with number of medical appointments) and surgery (i.e., requires some time for postoperative recovery). Then, the common acute side effects of chemotherapy, such as fatigue, anemia, and nausea, may further limit engagement in physical activity. A systematic review by Scott et al. [11] of 48 randomized controlled trials of aerobic exercise during adjuvant chemotherapy demonstrates a preservation of, or an improvement in, cardiorespiratory fitness especially in those with low initial values [11], while others report better improvement in those with higher initial values [12]. Aerobic exercise during adjuvant chemotherapy does not appear to stimulate preservation of the production of red blood cells [6, 13, 14] (Fig. 8.1), so improvements in

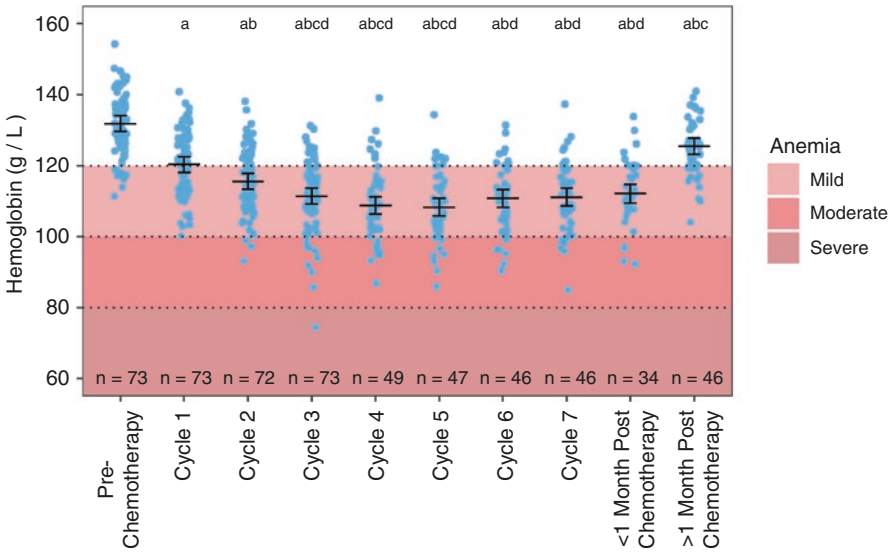

Fig. 8.1 Incremental changes in hemoglobin across chemotherapy cycles with gradual improvement with time after completion [6]. Legend: Bars denote mean and 95% confidence intervals. [a]Significantly different from prechemotherapy. [b]Significantly different from cycle 1. [c]Significantly different from cycle 2. [d]Significantly different from >1 month after chemotherapy

cardiorespiratory fitness are contingent on other central (i.e., cardiac function) and peripheral adaptations (i.e., improved uptake and utilization of oxygen by skeletal muscle) [5, 15].

Specific to *muscular strength*, loss of muscle strength and endurance is common due to deconditioning or as a side effect of cancer treatment. A systematic review of 21 meta-analyses on randomized clinical trials in cancer survivors by Fuller et al. [16] reported an increase in upper and lower body muscular strength with resistance training in early-stage cancer survivors. Specific to during chemotherapy, the pooled effects were similar for interventions both during chemotherapy and after chemotherapy. The majority of research was in women with early-stage breast cancer but also included individuals with hematological cancers. Of note, in older adults, neuromuscular contributions explain up to 50% of variation in muscle strength; thus, in the context of chemotherapy, resistance training may still effectively improve muscle strength in the absence of gains in muscle mass [8, 17].

Specific to *body composition*, maintenance of body weight can be difficult during treatment for some cancers, where loss of weight and lean body mass are a common concern, such as advanced cancer in the colon, lung, and pancreas [18]. In contrast, weight and fat mass gain can be a common side effect of chemotherapy and anti-estrogen therapy for breast cancer [19]. In cases where weight and lean body mass loss may be a side effect of treatment, the fitness professional should ensure that exercise training is not creating an excess energy deficit (i.e., energy expenditure exceeds adequate dietary energy and nutrient intake) that contributes to weight loss and can aggravate fatigue [20, 21]. Working with a trained oncology dietician who can advise on dietary modifications that would support adequate fuel availability and replacement during and post exercise, respectively, may be prudent [8]. Obesity is a risk factor for multiple cancers, including postmenopausal breast, renal cell and endometrial cancer; thus these survivors are more likely to be overweight or obese at the time of diagnosis [22]. For patients who are overweight or obese, the exercise professional should be aware of the safety considerations related to exercise, including orthopedic limitations to weight-bearing exercise and potential for coexistence of cardiovascular disease risk factors [23, 24]. If weight loss is a health goal for these individuals, it may be prudent for the exercise professional and/or survivor to partner with a registered dietician to provide dietary recommendations that can complement an exercise program and also support ongoing needs related to cancer treatment [8].

Specific to *musculoskeletal flexibility*, surgery can result in temporary or more permanent reductions in joint range of motion and extensibility of muscle, tendon, fascia, and skin. Exercise professionals should be aware of surgical sites, and if abnormal movement patterns are observed, adapt the proposed movements to avoid placing abnormal strain on other body structures, and consider referral to physical therapy in efforts to address restrictions [8].

The 2019 ACSM Roundtable Guidelines on Exercise for Cancer Survivors [8] in general support the current Physical Activity Guidelines for Americans, which state that adults should avoid inactivity and aim to do at least 150–300 minutes per week of moderate-intensity or 75–150 minutes a week of vigorous-intensity aerobic

physical activity and muscle strengthening activities on 2 or more days a week [25]. However, the 2019 ACSM Roundtable Guidelines on Exercise for Cancer Survivors reported that cancer survivors can see benefits on common side effects, namely, anxiety, depressive symptoms, fatigue, physical functioning, and health-related quality of life, with lower levels of activity, namely, 30–60 minutes of aerobic exercise 2–3 days per week or 20–40 minutes of aerobic exercise combined with resistance training 2–3 days per week [8]. This level of exercise may be especially relevant for individuals concurrent with receiving infusion therapy.

What Is the Ideal Exercise Prescription During Infusion Therapy?

There are very few trials that provide a head-to-head comparison of different types of exercise or volumes of exercise during chemotherapy. A landmark trial published by Courneya et al. [26] in 2007 was the first randomized controlled trial of exercise specifically *during* adjuvant chemotherapy for women with early-stage breast cancer. Women were randomized to supervised aerobic exercise (n = 78), supervised resistance exercise (n = 82), or usual care control group (n = 82). The intervention took place for the length of each person's chemotherapy treatment and the average duration was 17 ± 4 weeks. The intervention was three sessions per week and attendance was 72% in the aerobic group and 68% in the resistance group. Aerobic fitness (VO_2 peak) was maintained in the aerobic group (+0.2 mL/kg/min) in comparison with statistically significant reductions in the resistance group (−1.4 mL/kg/min) and control group (−1.6 mL/kg/min). In the resistance group, there was a statistically significant increase in upper (+8.8 kg) and lower (+8.2 kg) body strength using 1-repetition maximum compared to the aerobic group (+2.6 kg and + 3.3 kg, respectively) and control group (+1.5 kg and + 1.4 kg, respectively). There were also positives changes in cancer-specific quality of life, fatigue, depression and anxiety in the exercise groups, but this did not reach statistical significance compared to the control group. This trial demonstrated the safety of both aerobic and resistance exercise during chemotherapy and provided early insight into the potential specific benefits of each type of exercise training that was possible during chemotherapy.

Based on the clear benefits of exercise relative to usual care seen in the first trial, Courneya et al. [27] then compared the impacts of exercise volume or type during adjuvant chemotherapy. Women with early-stage breast cancer were randomized to 3 days per week of supervised exercise at the "standard" dose (25–30 min of aerobic exercise per session) (n = 96), "high" dose (50–60 min. of aerobic exercise per session) (n = 101), or "combined" dose (50–60 min. of aerobic exercise, combined with resistance exercise) (n = 104). Adherence to the number of aerobic sessions prescribed was 88% (standard), 82% (high), and 78% (combined), and individuals in the combined group attended 66% of prescribed resistance training sessions.

Compared to the "standard" dose, the "high" and "combined" dose resulted in a lower reduction in self-report physical function during chemotherapy, indicating a greater dose of either aerobic alone or combined with resistance exercise provided additional benefits to the standard dose of aerobic only training. In confirmation of the importance of the training principle of specificity in cancer populations, the "combined" dose led to greater strength gains in upper and lower body (+5.7 and + 8.6 kg, respectively in 1-RM testing) than the "standard" (+1.7 and + 2.5 kg, respectively) or "higher" dose interventions (0.0 and + 2.5 kg, respectively), both of which did not include resistance training. Likewise, the "higher" (aerobic) dose resulted in a lower reduction in aerobic fitness during chemotherapy (−2.5 mL/kg/min) than the "combined" (−3.6 mL/kg/min) or "standard" dose (−3.4 mL/kg/min) interventions that involved less aerobic duration.

The comparison of supervised versus home-based exercise during chemotherapy has also been examined in women with early-stage breast cancer during adjuvant chemotherapy. Van Waart et al. [28] randomized women to "Onco-Move" (a low-intensity, aerobic, home-based exercise program, n = 76), "On-Track" (a moderate-to-high intensity, supervised, aerobic and resistance exercise program 2 days per week, plus home-based activity, n = 77) or a "usual care" control group (n = 77). Participants in both exercise groups were encouraged to aim to be active 5 days per week. Those in the supervised "On-Track" intervention attended 71% of twice-weekly supervised sessions, while 48% of the "On-Track" and 55% of the "Onco-Move" group self-reported that they followed the five times/week physical activity recommendations at least 75% of the time. At end of chemotherapy, the "Onco-Move" and "On-Track" exercise groups had less decline in cardiorespiratory fitness than the usual care group, as well as better physical function, less nausea and vomiting, and less pain. In addition, at the end of chemotherapy, the supervised "On-Track" intervention resulted in statistically less deterioration in cardiorespiratory fitness and muscular strength and less increase in fatigue compared to "Onco-Move" and usual care. This study demonstrated that a supervised program of combined aerobic and resistance exercise is potentially most effective at combating the common side effects of chemotherapy, including the observed decline in physical function, cardiorespiratory fitness, and muscle strength, as well as alter the magnitude of cancer-related fatigue. However, the authors also noted that if individuals are unable or unwilling to participate in a supervised program, a home-based program may still be of benefit.

How to Approach Exercise Prescription During Infusion Therapy?

The approach to prescribing exercise during chemotherapy continues to evolve secondary to both new research findings and the expanding experience of exercise professionals working with individuals with cancer. In contrast, there is insufficient research evidence at this time to provide a framework for exercise prescription

in individuals receiving immunotherapy. A summary of approaches to exercise prescription for individuals receiving chemotherapy for early-stage cancer is outlined below.

Standard Approach to Exercise Prescription Applied to Cancer Survivors

The most common approach to exercise prescription during chemotherapy has been an aerobic or combined aerobic and resistance exercise program that is linearly progressive in intensity and duration over time, consistent with the standard exercise training approach that is commonly used for the general population [29] (Fig. 8.2). However, an exercise prescription that linearly increases in intensity and duration may fail to account for the commonly observed fluctuations in patient-reported outcomes and physiological responses to chemotherapy. Rather than observing the expected improvements in fitness outcomes with a well-designed standard exercise prescription, a cancer patient may only maintain fitness or may decline in fitness despite engaging in exercise. A standard exercise prescription approach that does not heed the dose-dependent and potentially cumulative effects of chemotherapy on the physiological and psychological status of the patient may be less effective at improving health outcomes and cause discouragement when patients are unable to meet the prescription targets.

There are five parameters commonly used to describe the exercise prescription for an intervention or program [23]. These include frequency of exercise bouts per week, intensity of each exercise bout, duration of each exercise bout, the progression, or rate of increase of the other parameters, and the type of activity, such as aerobic or resistance exercise.

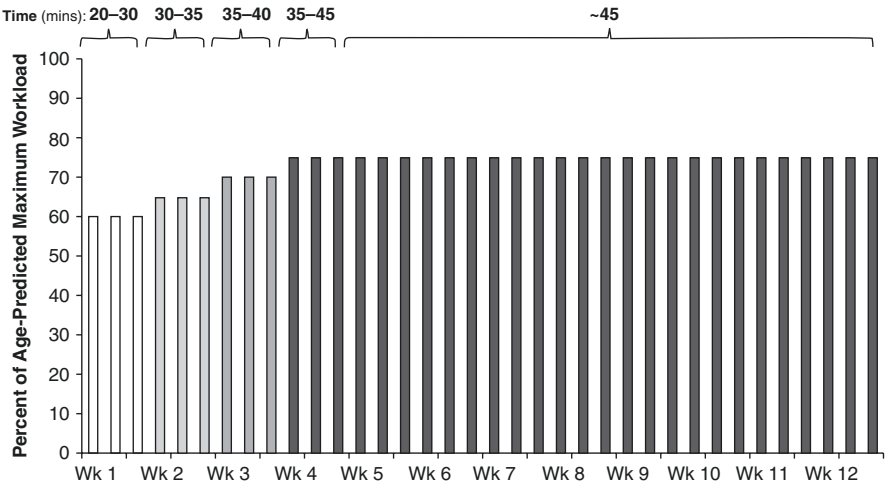

Fig. 8.2 Example of standard exercise prescription approach. (From Sasso et al. [30])

Frequency The majority of the exercise interventions during chemotherapy literature to date have used a supervised exercise frequency of 2 or 3 times per week, with many of the more recent studies supplementing the supervised sessions with encouragement of home-based exercise intended to work toward achievement of the 150 minutes per week of exercise recommended by the American College of Sports Medicine for all adults, including cancer survivors [8, 23]. However, adherence to supervised exercise frequencies of 2–3 times weekly during chemotherapy ranges from 64% to 83% [26–28, 31, 32].The common barriers to attendance of supervised sessions during chemotherapy treatment, which include treatment symptoms and conflicting appointments, can be difficult to avoid [33, 34]. Attendance of supervised exercise sessions decreases with increasing treatment dose likely due to accumulation of treatment symptoms (Fig. 8.3a). Therefore, behavioral support strategies to encourage exercise may be more important in later chemotherapy cycles [33]. In a home-based setting, several short bouts per day rather than one single bout can be a useful strategy during chemotherapy treatment [23].

Intensity The available literature and exercise guidelines suggest that moderate-to-vigorous-intensity aerobic and low-to-high-intensity resistance exercise is safe and

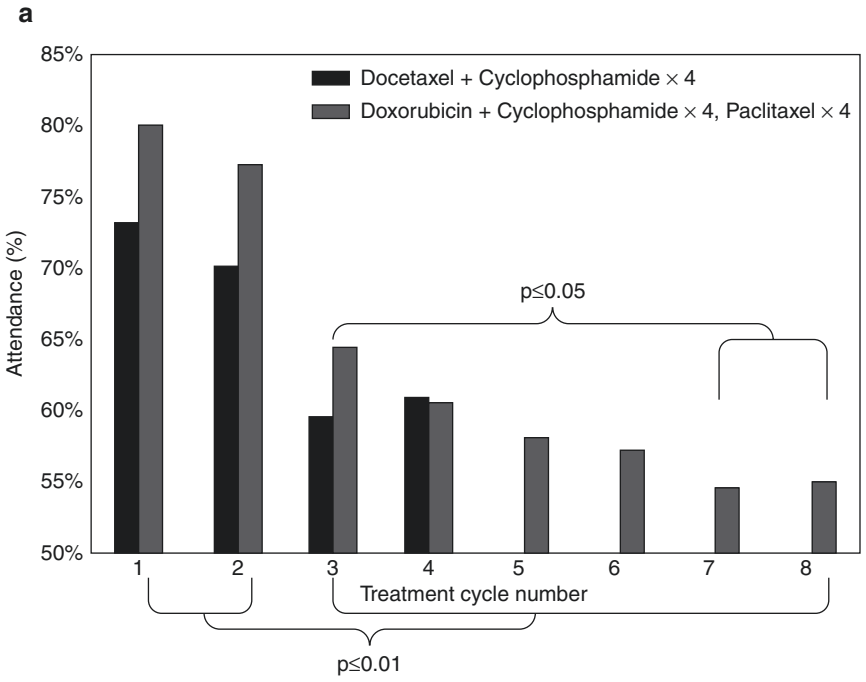

Fig. 8.3 (**a**) Comparison of attendance of supervised exercise between treatment protocols and across cycles. Adherence to intensity (**b**) and duration (**c**) for each step of progression over the first 12 weeks of an exercise intervention during adjuvant chemotherapy for breast cancer [33]

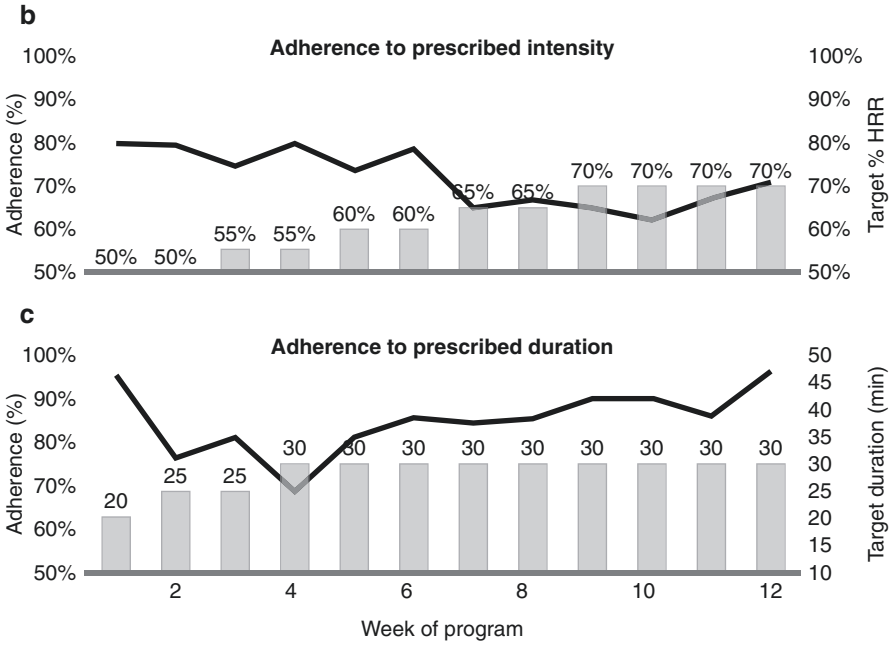

Fig. 8.3 (continued)

results in improvements in health-related outcomes [8]. However, on average, adherence to aerobic intensity tends to decrease at higher prescribed intensities [33] (Fig. 8.3b), indicating that this suggested range of intensity may not be appropriate or feasible for all patients and consistent with the philosophy of avoid inactivity, a lower intensity may also be of benefit. For resistance intensity, interventions can also start at initial low intensities and progress, especially for older individuals or for those without prior resistance training experience [23].

Time or Duration The current Physical Activity Guidelines for Americans recommends at least 150 total minutes of moderate-intensity aerobic exercise or 75 minutes of vigorous-intensity aerobic physical activity per week for all adults [25]. During chemotherapy treatment it may be a challenge for many patients to meet these exercise goals, due to fluctuations in treatment symptoms and interference of ongoing medical care. Bouts of aerobic exercise lasting 20–30 minutes, performed 2–3 times per week, may be sufficient to improve cancer-related anxiety, depression, fatigue, health-related quality of life, and physical function [8]. Most patients with early-stage cancers, even those who were previously sedentary, are commonly able to complete 20-minute aerobic exercise sessions, and with an appropriate length of progression (e.g., 2–5 weeks) can work up toward completing 30 minutes per session [33] (Fig. 8.3c).

Progression Over time, the body adapts to exercise, so in order to see continued improvement, the above components of the exercise prescription must be progressed. Available guidelines for cancer have included ranges for suggested frequencies, intensities, and durations, with the implied goal of progression over time within those ranges [8]. Most research exercise interventions during chemotherapy have reported a progressive linear increase in aerobic and/or resistance intensity, duration, or both, yet many fail to describe the progressions in detail [35–37]. Typically a progression in either intensity or duration every 1–2 weeks can be used if tolerated. It is important to keep in mind that not all patients are able to tolerate progressions in an exercise prescription during chemotherapy (Fig. 8.3b, c). Generally, these progressions take place without reference to the timing of chemotherapy infusions or with consideration of treatment symptoms. It is likely that chemotherapy at least blunts the exercise training response, so progressions may not be required as frequently, and may require specific timing with respect to infusions.

Proposed Novel Approaches to Exercise Prescription Specific for Cancer Survivors

"Bad Day" Adjustment There is an emerging appreciation that patients receiving chemotherapy treatment may experience fluctuations in acute side effects of chemotherapy treatment within a chemotherapy cycle. This may require a reduction in intensity or duration of the exercise prescription [8, 23]. Indeed, one of the landmark randomized controlled trials of exercise during chemotherapy by Courneya et al. [38] described making alterations to the exercise prescription, as needed, in a non-standardized approach. Kirkham et al. [33] evaluated a standardized approach for adjusting the prescription for a given exercise session within a standard linear exercise prescription to accommodate for the dynamic nature of chemotherapy side effects. On "good days" when the patient was generally feeling well, the prescribed aerobic intensity and duration followed the standard linear progression of the exercise prescription. On "bad days," where the participant reported, upon arrival to the exercise facility, feeling particularly unwell, the aerobic exercise intensity was preemptively reduced by 10 percentage points of heart rate reserve (HRR). For example, if the prescribed intensity for that day was 65–70% HRR, a new target heart rate was calculated for that day for 55–60% HRR. Then, for the following exercise session, the prescription would return to the standard linear prescription unless the participant still reported feeling unwell. The aerobic intensity prescription was adjusted based on the research team's previous observation that adherence to the prescribed intensity of an aerobic exercise prescription is often the most difficult element of the exercise prescription during chemotherapy. No adjustments for resistance training were designed into the intervention, as issues of progression of resistance training had not been observed. In a single-arm trial of exercise as part of standard of care for women receiving adjuvant chemotherapy for early-stage breast

cancer, during chemotherapy and radiation treatment combined, 206 of 2779 (7.4%) completed aerobic exercise sessions required an adjustment to the prescription due to a "bad day" for treatment symptoms [33]. Similar standardized adjustments were made to the aerobic intensity prescription in other cases including for individuals taking beta-blockers, if an individual consistently reported the prescription was too difficult, presence of self-reported asthma symptoms, extended gym absence, and other illness (e.g., cold). Participants were able to adhere to the new prescription in 68% of the sessions with an adjusted prescription, and the average RPE did not differ between adjusted and non-adjusted sessions [33]. The use of the "bad" day adjustment also assisted with improving attendance to the supervised intervention, as individuals knew that an adjustment was possible if they were feeling unwell. This suggests that using a reduction of 10 percentage points of HRR as a standardized adjustment in aerobic exercise intensity was an appropriate size of adjustment and effectively maintained a similar subjective assessment of exercise challenge for the patient on their "bad day."

Nonlinear Training Sasso et al. [30] proposed a non-linear approach to aerobic exercise prescription for cancer survivors that takes into account the training principles of individualization, specificity, overload, rest, and recovery. This takes a format to the exercise prescription where both sessions within a week and across the weeks vary between low-intensity (e.g., 55% VO_2 peak) and moderate- (e.g., 75% VO_2 peak) and high-intensity (e.g., 100% VO_2 peak) training in a progressive manner with the goal of targeting various physiological systems (Fig. 8.4). Sessions with high relative intensity in turn have a shorter duration and are less frequent to ensure recovery between sessions. One published RCT to date has compared the efficacy of a traditional linear

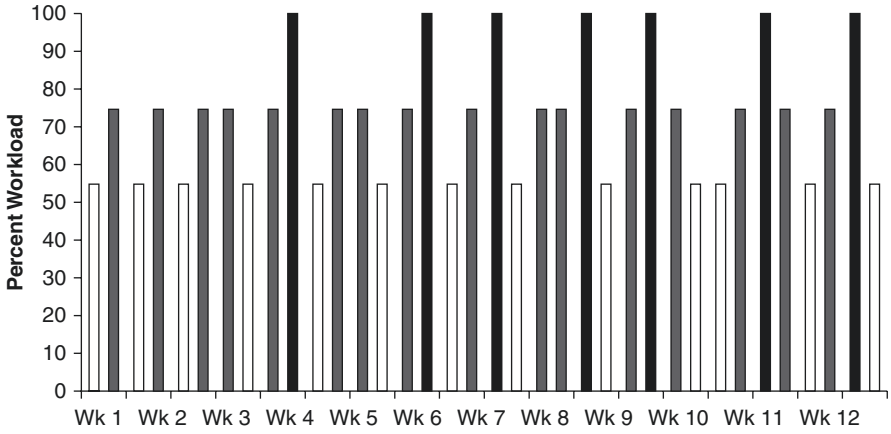

Fig. 8.4 Example of non-linear exercise prescription approach. (From Sasso et al. [30]). Legend: Sessions and weeks progress over the course of the prescription and vary between low intensity (e.g., 55% VO_2 peak; white bars) and moderate (e.g., 75%; gray bars) and high intensity (e.g., 100% VO_2 peak; black bars)

approach to a non-linear approach. In women following chemotherapy treatment for early stage breast cancer, Scott et al. [39] reported only modest improvements (≤ 0.8 ml/kg/min) in peak aerobic capacity with either prescription approach compared to attention control group, and the non-linear approach improved all patient-reported outcomes compared to control, with only an improvement in self-reported fatigue in the traditional linear group. There are several other studies that have compared a non-linear exercise prescription to usual care in cancer populations which demonstrate a low adverse event rate, good tolerability, and favorable benefits on VO_2 peak, quality of life, and other physiological outcomes [30]. Fairman et al. [40] further recommended use of a non-linear approach for resistance exercise prescription in oncology populations based on efficacy demonstrated in non-cancer populations and incorporation of an exercise prescription approach that has greater attention to principles of exercise training. Furthermore, Fairman et al. [40] also suggest the use of a technique called autoregulation that would allow for flexibility in the daily choice of repetitions, sets, and weight with fluctuations in patients' readiness to train within a non-linear exercise prescription approach. This approach in particular could be useful in the context of chemotherapy treatment, where readiness to train will be influenced by fluctuations in treatment symptoms. However, this remains to be tested in individuals with cancer.

Chemotherapy-Periodized Training A more specific approach to the incorporation of non-linear exercise prescriptions for patients receiving chemotherapy is the periodization of a training period around the cycle length and typical symptom profile associated with a given chemotherapy treatment regimen [41]. Periodization is an organizational approach to aerobic and resistance training that is often used in high performance and healthy populations to prevent overtraining or injury that involves short cycles or "periods" of systematic variation in training specificity, intensity, and volume [42]. It has also been reported that a periodized approach to exercise prescription is safe and appropriate for previously sedentary non-cancer populations [43]. Given the cyclical variations in the infusion schedule of chemotherapy and associated symptom response, an exercise prescription with periods that correspond to the length of a chemotherapy treatment cycle may be a successful approach to (1) enhance exercise adherence during the time of greatest acute side effects of chemotherapy and (2) optimize completion of greater exercise dose to maximize training adaptations, and thereby health benefits, in the remaining time in the cycle (Fig. 8.5). Admittedly, this approach would work best with chemotherapy regimens with 2–3 week cycle lengths and would be more challenging to incorporate with regimens of weekly chemotherapy infusions. As previously mentioned, the peak and duration of chemotherapy side effects following a chemotherapy infusion vary from patient to patient but are most common within the first week following a chemotherapy infusion. Notably, greater patient-reported fatigue and feelings of depression, as well as objective measures of elevated resting heart rate, reduced blood pressure, and greater sleep disruptions have been reported in the week following chemotherapy treatments [6, 44, 45]. During this time, the patient may have a reduced physical capacity or motivation to exercise. This timeframe also corresponds to peak of activity of most chemotherapy agents within the body, before being cleared from the body after the first week [46].

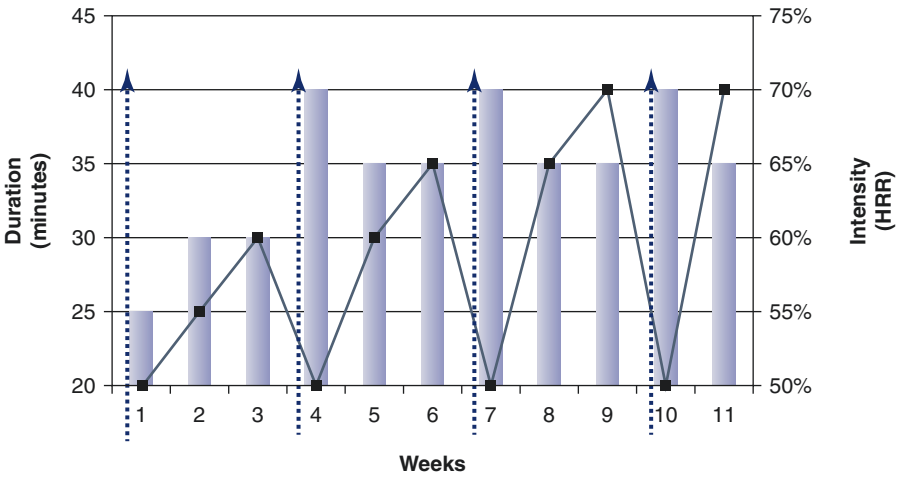

Fig. 8.5 Example of chemotherapy-periodized exercise prescription. Legend: Timing of chemotherapy infusions in dotted lines; intensity in black lines; duration in gray bars

The confluence of patient-reported symptoms, physiological disruptions, and pharmacokinetics of treatment suggests that lower intensity aerobic exercise in the first week after chemotherapy infusion may be ideal. During this window of time, a lower intensity may be less likely to exacerbate acute side effects, such as nausea or fatigue, or exacerbate the increase in oxidative stress produced by chemotherapy. Following this week, most patients experience steady improvements in their symptoms and the noted physiological disruptions. The result is then a period of relative recovery before their next chemotherapy treatment [6, 44, 45]. The periodization structure could consist of a standardized or patient-specific length of time after each treatment (e.g., 5–8 days) that consists of lower aerobic intensity, but increased duration, to maintain load and minimize deconditioning. Then, in the remaining days of the treatment cycle (e.g., ~1–2 weeks depending on the regimen), the training principles of progression and overload could become the focus while still taking into account the overall health status and well-being of the patient (e.g., it is likely that even in the period of time of reduced side effects, training-induced adaptations are slower requiring a slower rate of progression than typical). This approach has been trialed in a small pilot study by Bland et al. [47] Preliminary results demonstrated higher attendance of supervised exercise sessions with a chemotherapy-periodized approach than in previous studies using a standard linear exercise prescription approach.

High-Intensity Interval Training High-intensity or aerobic interval training has received an abundance of recent attention for being a time-efficient and effective aerobic exercise training approach for healthy individuals and some clinical populations [48, 49]. In 2014, Hornsby et al. [50] incorporated a single weekly session of high-intensity interval training in the last 3 weeks of an exercise program during

neoadjuvant chemotherapy for 10 early-stage breast cancer patients. The overall program involved a gradual progression in aerobic intensity and duration, as well as incorporation of training at ventilatory threshold in the weeks prior to the introduction of interval training. The intervals consisted of 30 seconds at 100% of peak workload on a cycle ergometer determined from the pre-chemotherapy maximal exercise test, followed by 60 seconds of active recovery for 10–15 repetitions. Adherence data and adverse events were not reported specifically for the interval sessions. However, the overall attendance was high at 82%. However, at least one patient did not attend at all, leaving a potential of nine women who may have performed the intervals. Only one adverse event was reported during exercise and was quickly resolved.

Mijwels et al. [14, 51] compared two high-intensity aerobic interval training (HIIT) interventions to a usual care control group in early-stage breast cancer patients during adjuvant chemotherapy. The HIIT protocol was 3 × 3 minute intervals on a cycle ergometer at a rating of perceived exertion of 16–18, with 1 min lower intensity "rest" in between. The HIIT protocol was combined with resistance training ("RT-HITT" group) or 20 minutes of moderate-intensity aerobic exercise on a cycle ergometer (AT-HIIT). The intervention was 16 weeks in length with two supervised sessions per week for the RT-HIIT and AT-HIIT groups. No adverse exercise-related events occurred. Attendance at supervised sessions was 68% for the RT-HIIT and 63% for the AT-HIIT groups and adherence to the prescribed exercise at each session was 83% for RT-HIIT and 75% for AT-HIIT. While both exercise interventions prevented the significant increase in cancer-related fatigue and attenuated the decrease in physical functioning that occurred in the usual care group, the RT-HITT reduced total symptom burden, while the AT-HITT just maintained this score [51]. Additionally both exercise interventions prevented the significant decline in predicted VO_2 peak and increase in body weight that occurred in the usual care group [14]. RT-HIIT was superior to AT-HIIT for both upper and lower body muscular strength. In terms of overall benefits, the RT-HIIT intervention that included both aerobic interval training and resistance training was superior to the AT-HIIT intervention that included additional aerobic training in lieu of resistance training. These findings suggest that HIIT is potentially feasible and safe in women with early-stage breast cancer during adjuvant chemotherapy, but more research is needed to further the understanding on the optimal way to integrate HITT into exercise prescriptions for cancer survivors.

While some data are available regarding feasibility, safety, and efficacy of these novel approaches to exercise prescription during chemotherapy treatment, there is no enough evidence to recommend one approach over another. The optimal prescription for a given individual with cancer who is receiving chemotherapy treatment requires a balance of patient tolerance with the goal of the program specific to addressing elements of physical fitness and quality of life.

What Safety and Logistical Considerations to Keep in Mind?

During infusion therapy, working closely with the oncology treatment team is recommended, as treatment approaches change frequently and understanding the side effects of newer treatments continues to evolve [8]. The impact of infusion therapy on exercise tolerance and response to a given exercise stimulus may vary due to the direct effects of cancer treatments on physiological systems (i.e., anemia), side effects of cancer treatment (i.e., cancer-related fatigue may lower exercise tolerance), and demographics factors (i.e., age), along with the pre-diagnosis health and functional capacity of the individual [8, 52].

Pre-participation screening individuals with cancer for participation in exercise during infusion therapy is a relevant consideration. The ACSM pre-participation guidelines for evaluating the need for medical clearance for non-cancer comorbidities should be applied in cancer survivors to minimize risks of adverse exercise-related events [23]. The ACSM pre-participation guidelines do not explicitly address risks for adverse events and/or injury during exercise that is specific to the adverse effects of cancer treatment. The 2019 ACSM Expert Consensus Statement on Exercise Guidelines for Cancer Survivors refers to the National Comprehensive Cancer Network (NCCN) Survivorship Guidelines [53] to frame recommendations for when medical clearance and/or further medical evaluation by a medical professional is indicated as well as the level of supervision during exercise training for cancer survivors to ensure safety based on the disease and treatment-related side effects (Table 8.3) [8]. Following pre-participation screening, requiring a comprehensive physical fitness assessment prior to starting exercise may create an unnecessary barrier to starting activity. For this reason, the 2019 ACSM Expert Consensus Statement on Exercise Guidelines for Cancer Survivors states that no assessments are required to start low-intensity aerobic training (i.e., walking or cycling), resistance training with gradual progression, or a flexibility program in most cancer survivors. Medical clearance may still be indicated as previously described depending on exercise and health history and presence of cardiovascular, renal, or metabolic symptoms prior to starting a moderate-to-vigorous aerobic exercise program [23].

The 2019 ACSM Expert Consensus Statement on Exercise Guidelines for Cancer Survivors [8] agreed with the overall conclusion from the 2010 ACSM Roundtable on Exercise Guidelines for Cancer Survivors that exercise is generally safe for cancer survivors [54]. However, it is important to understand that the majority of available evidence on the safety and efficacy of exercise during and following cancer treatment is derived from RCTs of supervised and/or home-based prescribed exercise and trials in early stage breast cancer survivors [55–57]. RCTs also commonly enroll individuals who are healthier, with higher physical function and exercise motivation and experience. Therefore, the results from these studies may not be fully generalizable to the broader population of cancer survivors [23]. Exercise professionals should use their clinical judgment within their scope of practice to

Table 8.3 Adapted national comprehensive cancer network triage approach based on risk of exercise-induced adverse events [8]

Description of patients	Evaluation, prescription, and programming recommendations
No comorbidities	No further pre-exercise medical evaluation[a] Follow general exercise recommendations
Peripheral neuropathy, arthritis/musculoskeletal issues, poor bone health (e.g., osteopenia or osteoporosis), lymphedema	Recommend pre-exercise medical evaluation[a] Modify general exercise recommendations based on assessments Consider referral to trained personnel[b]
Lung or abdominal surgery, ostomy, cardiopulmonary disease, ataxia, extreme fatigue, severe nutritional deficiencies, worsening/changing physical condition (i.e., lymphedema exacerbation), bone metastases	Pre-exercise medical evaluation[a] and clearance by physician prior to exercise Referral to trained personnel[b]

[a]Medical evaluation – per NCCN guidelines for specific symptoms and side effects [53]
Legend: [b]Rehabilitation specialists (i.e., physical therapists, occupational therapists, physiatrists) and certified exercise physiologists (i.e., American College of Sports Medicine Certified Clinical Exercise Physiologist (ACSM-CEP), Canadian Society for Exercise Physiology Certified Exercise Physiologist (CSEP-CEP), Exercise & Sport Science Australia Accredited Exercise Physiologist (ESSA-AEP)).

assess safety of each individual client in developing and exercise prescription and monitoring the response of the client to the exercise prescription. Physical therapy or medical evaluation may be warranted as a bridge to inform appropriate modifications to an individual's exercise program and/or treat toxicities, impairments, and limitations that prevent a cancer survivor from working toward recommended levels of exercise [23].

In developing an exercise prescription and encouraging adherence to the prescription, exercise professionals should be aware of and respectful of the fact that individuals diagnosed with cancer commonly have many concerns, such as life expectancy, employment issues, and family matters, that may limit prioritization of exercise in their lives [8]. A key consideration is to focus the exercise prescription on each individual client's goals. A customized program may not yet resemble or reach the exercise programs recommended in these guidelines, such that a goal may be to strive toward preparing the client to engage in recommended types and levels of exercise over their lifetime as outlined in the 2018 Physical Activity Guidelines for Americans [58].

Specific to infusion therapy, there are some unique issues with exercise during chemotherapy including changes in blood counts or issues of dehydration and low energy intake which are common due to symptoms of nausea or vomiting [59]. If possible, it is helpful to review the client's recent blood counts either through approved access to the medical record or by asking the patient to provide the trainer

Table 8.4 Factors to monitor for exercise participation during cancer treatment

	Precaution requiring physician approval	Consideration
General	Pain	Investigate any new onset of pain; modify exercise to avoid exacerbations of existing pain
Chemotherapy/ targeted therapy	Platelets <50,000	Avoid activities that increase risk of injury (falling), bruising or bleeding. Check with physician on safety of exercise beyond activities of daily living
	White blood cells <3000	Avoid public facilities where risk of exposures to bacteria are high; adhere to infection control guidelines
	Hemoglobin <10 g/dl	Prescribe only low-intensity-type activities (e.g., easy walking) or activities performed for shorter periods of time and more frequently; allow for adequate rest/recovery
	Febrile illness >100° Fahrenheit	No formal exercise training; avoid exercise until asymptomatic by >48 hours
	Vomiting or diarrhea	
	Peripheral neuropathy: Loss of sensation and poor balance	Avoid free weights and treadmill, use well supported positions for exercise
	Osteopenia/ bone issues	Avoid high impact exercise
Radiotherapy	Cancer-related fatigue	Closely monitor response to exercise
	Severe tissue reaction in region	Avoid exercises that compromise the skin and tissue in the region

Reference: Need to get from ACSM Clinical Exercise Phys book

with latest blood count values taken as part of routine medical care. There are some blood values and symptoms for which exercise may be contraindicated and review by a physician is warranted prior to continuing (Table 8.4). Resting and exercise blood pressure values may also vary more during treatment, and hypotension is common [6]. Feeling lightheaded or dizzy when changing body positions can be common due to the issue of hypotension and dehydration, so clients should be advised to change positions slowly, especially after exertion (i.e., such as standing up from a leg press machine), to avoid putting their head below their heart (i.e., to bend down to pick up weights off the ground) and to perform gradual warm-up and cool-down before and after aerobic training sessions [59]. In the case of hypotension causing additional symptoms, exercise professionals could also provide general recommendations for the management of autonomic or orthostatic intolerance disorders, such as ensuring adequate hydration, increasing salt intake, and avoiding bed rest [60], along with the suggestion that the client discuss this issue further with a medical professional.

A stem cell transplant is a unique type of cancer treatment that can be used to treat some blood-related cancers, such as leukemia, lymphoma, and multiple myeloma, or for individual treated with high-dose chemotherapy or radiation. Stem

cells are the most basic cells in the bone marrow: the production center of blood cells. Stem cells can be harvested from the individual needing the treatment (autologous) or a donor (allogeneic). For hematological cancers, a key part of the treatment is the use of high-dose chemotherapy to ensure the original stem cells in the bone marrow are essentially destroyed before healthy new stem cells are transplanted into the bone marrow space to allow new blood cells to develop. Individuals are hospitalized for the high-dose chemotherapy treatment and require isolation due to a weaken immune system until the new bone morrow is transplanted and functioning well. While exercise has been shown to be beneficial during the process of a stem cell transplantation [61, 62], how to prescribe exercise in this setting is a specialized skill and beyond the scope of this chapter.

Infusion therapy can also be used for individuals with advanced cancer, namely, cancer that has metastasized. In these cases, chemotherapy or immunotherapy may be used to slow down cancer growth, but the goal may not be to cure the cancer. Metastases can be located in a variety of tissues, including other organs and bones. Exercise can be safe and effective for individuals with advance cancer, but how to prescribe exercise in this setting is a specialized skill and beyond the scope of this chapter. Special attention to prescribing exercise is needed for individuals with bone metastases, particularly if the location of the metastases is in the vertebrae, pelvis, or long bones (i.e., femur or humerus).

Adaptations to the exercise prescription secondary to the specific side effects of infusion therapy may be required. Special considerations and modifications to exercise

Table 8.5 Additional adapted exercise programming considerations for individuals during infusion therapy [8]

Consideration	Recommendations
Older adults	Physical problems reported by cancer survivors, such as cognitive difficulty, neuropathy, sarcopenia, muscle weakness, slowing, and fatigue, may be similar to those of older people without cancer, but cancer treatment can accelerate these declines Exercise professionals will need to combine ACSM guidelines on exercise programming for older adults [63] with the recommendations in this publication Integrate fitness and functional assessments prior to beginning an exercise program to more accurately determine baseline functional abilities
Ostomy	Empty ostomy bag before starting exercise Weight lifting/resistance exercises should start with low resistance and progress slowly under the guidance of trained exercise professionals. People with an ostomy may be at an increased risk of parastomal hernia. To regulate intra-abdominal pressure, correct lifting technique and good form are required. Avoid use of a Valsalva maneuver [64, 65] Modify any core exercises which cause excessive intra-abdominal pressure, namely a feeling of pressure or observed bulging of the abdomen Those with an ileostomy are at increased risk of dehydration. Get medical advice on ways to maintain optimum hydration prior, during, and after exercise Those doing contact sports or where there is a risk of a blow to the ostomy may wish to wear an ostomy protector/shield

Table 8.5 (continued)

Consideration	Recommendations
Peripheral neuropathy	Stability, balance, and gait should be assessed before engaging in exercise; consider balance training as indicated Consider alternative aerobic exercise (stationary biking, water exercise) rather than walking if neuropathy affects stability or use treadmill with safety handrails Resistance training recommendations: Monitor discomfort in hands when using hand-held weights Consider using dumbbells with soft/rubber coating, and/or wear padded gloves Consider resistance machines over free weights [66]
Stem cell transplantation	Home-based exercise encouraged A full recovery of the immune system recommended before return to gym facilities with the general public Start with light intensity, short durations but high frequency and progress slowly Exercise volume (intensity and duration) should be adapted on a daily basis based on the individual's presentation
Symptom clusters	Symptoms and side effects of cancer treatment rarely appear in isolation**;** rather**,** symptom clusters are the norm (i.e., fatigue, pain, sleep disturbance), especially during cancer treatment and in those with advanced disease [67] Exercise professionals must be aware of this complexity and be prepared to refer clients/patients back to the medical team (i.e., rehabilitation or oncology physician, general practitioner, or nurse) for review and management of symptoms when safety concerns develop or when target symptom (e.g., fatigue) is not responding as expected

programs have been adapted from the NCCN guidelines (Table 8.5). For example, if an individual is experiencing issues with balance or discomfort due to peripheral neuropathy in their feet, an exercise professional should adjust the exercise prescription to accommodate for this. Using a cycle ergometer may reduce the risk of a fall due to reduced balance, or friction on the soles of the feet from walking on a treadmill.

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Chapter 9
During Radiation Therapy

Joachim Wiskemann

Background

Radiotherapy has been used to treat cancer for over a hundred years. Even today, radiation therapy still plays an important role in cancer treatment. Meanwhile, treatment approaches have become increasingly sophisticated: Today, tumors can be irradiated much more precisely than just a few decades ago. Radiation therapy uses high-energy particles or waves, such as X-rays, gamma rays, electron beams, or protons, to destroy or damage cancer cells. Radiation works by making small breaks in the DNA inside the cells. These breaks keep cancer cells from growing and dividing and cause them to die. Normal/healthy cells nearby can also be affected by radiation, but most recover and go back to working the way they should [2]. To allow healthy cells enough time to repair DNA damage, the radiation dose is divided into several individual sessions (fractions). The radiation dose is given in so-called Gray (Gy). This unit of measurement is named after the British physicist and father of radiobiology, Louis Harold Gray. As a rule, the total radiation dose, with the aim of destroying the tumor, is between 40 and 70 Gray. This total dose is normally divided into fractions of 1.8–2 Gy each (norm fractionation). This ensures good tolerability and reduces the risk of permanent damage and late complications. In comparison to chemotherapy, radiation is usually a local treatment. However, full-body irradiation is only used in some hematological malignancies. More than a half of all cancer patients receive radiation therapy which is used to shrink the size or to completely eradicate the tumor. There are various treatment settings where radiotherapy is used. Within some treatment regimens, a few cycles of chemotherapy may be given first, followed by radiotherapy. Other treatment approaches use radiotherapy before

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surgery to shrink the tumor (neoadjuvant therapy), or after surgery to help keep the cancer from coming back (called adjuvant therapy). Further, there are other treatment approaches where radiotherapy is given in combination with chemotherapy (radio-chemotherapy) [2].

As partially mentioned before, radiotherapy is used to cure or shrink the tumor, to prevent cancer recurrence or to treat symptoms caused by advanced cancer/metastases. In the last case, radiation might help relieve problems like pain, trouble swallowing or breathing, or bowel blockages that can be caused by advanced cancer.

Radiotherapy is mainly applied externally using machines to direct high-energy X-rays from outside the body into the tumor. Most people get external radiation therapy over 2–6 weeks in an outpatient setting. Internal radiation, called brachytherapy, is less often applied but routinely used in cervix, prostate, and breast melanoma patients (but can also be applied in a variety of other cancers). When using brachytherapy, a radioactive source is put inside the body into or near the tumor, which intensifies the applied radiotherapy dose. A third way to apply radiotherapy is by using a systemic approach where radioactive drugs are enabled to connect to certain tumor cell receptors. While connecting to those cells, the radiation effect will be activated and irradiate this particular area [2].

Despite its beneficial role, it is known that radiation therapy can slightly raise the risk of getting another type of cancer and a number of other side effects are associated with cancer irradiation, with cancer-related fatigue (CRF) being the most common one [37]. Furthermore, radiotherapy can lead to skin problems, hair loss, low blood counts, eating problems (when irradiation is taking place in the mouth or throat region), or digestive problems (if stomach or intestines are targeted regions). This could also lead to soreness in mouth or throat, nausea, vomiting, or loss of appetite. Radiation side effects often start during the second or third week of treatment depending on the prescribed dose and schedule. Most side effects disappear within a few months of ending treatment [21].

With a particular focus on radiotherapy-related side effects and exercise oncology, a recent observational study has shown that thoracic radiotherapy significantly affects respiratory function and exercise capacity in patients with breast cancer. Three months after treatment completion (total radiotherapy dose was about 50.4 Gy), significant decreases were observed in respiratory muscle strength, chest wall mobility, exercise capacity, and pulmonary function test results [53]. In combination with the abovementioned fatigue symptom being one of the most common side effects of radiotherapy, there is a strong rationale to implement physical activity interventions during radiotherapy. However, there are only few studies in the field of exercise oncology particularly dealing with radiotherapy setting. Therefore, the current chapter aims at summarizing the evidence for exercise interventions during curative and palliative radiotherapy, discusses potential mechanisms through which exercise can contribute to a better radiotherapy outcome, and finally provides exercise recommendations based on the current literature.

Evidence for Exercise Oncology during During Curative Radiotherapy

Breast Cancer

Radiotherapy in early-stage breast cancer patients is used in the adjuvant therapy setting to reduce the risk of relapse after surgery. The procedure is particularly important after breast-conserving therapy. After mastectomy or in situations where pre- and early forms of breast cancer are present, the decision for or against post-operative radiation depends on the individual benefit of the patient. Depending on previous treatment results and breast tumor proliferation, the entire diseased breast or only a part of it is irradiated. Depending on the disease status, also lymph nodes in the armpit or under the clavicle can be irradiated. Most breast cancer patients start with adjuvant radiation about 4–6 weeks after surgery, rarely later. It is mandatory that the surgical wound has healed prior to starting radiation therapy. Wound healing disorders or an infection in the surgical area can delay the onset of radiotherapy [24].

Evidence of Exercise – Radiation and Breast Cancer

A recent meta-analysis with the goal to explore the capability of exercise intervention to reduce fatigue during radiotherapy was able to identify nine randomized controlled trials [27]. Three out of nine studies investigated low-intensity mind–body exercise [8–10], whereas the others explored the effects of aerobic exercise [13, 38], machine-based resistance training [52], or a combination of aerobic and resistance exercise [5, 22, 35]. The majority of the studies compared the exercise intervention with usual care, and three studies offered their control group an active program like stretching [13], relaxation training [52], or range-of-motion exercises [22]. Seven studies offered supervised exercise programs and two delivered home-based interventions [13, 38]. Analysis based on 738 early-stage breast cancer patients revealed that the applied exercise interventions were statistically more effective at reducing fatigue than the control intervention (SMD – 0.46). The same but non-significant effect was shown for quality of life (SMD 0.46); see Fig. 9.1 [27].

Subgroup analysis with regard to the mode of exercise delivery revealed that those seven studies exploring the effect of supervised exercise interventions on fatigue were able to induce a medium-sized and significant reduction in fatigue in favor of the exercise groups (SMD – 0.46). However, statistical heterogeneity was large. Comparable but non-significant effects were seen for patients performing their exercise program at home [27].

In contrast to the previously described work, which focused on aerobic exercise, there is one study that has investigating resistance training vs. relaxation trainings, which showed a small-sized significant reduction in fatigue in favor of the

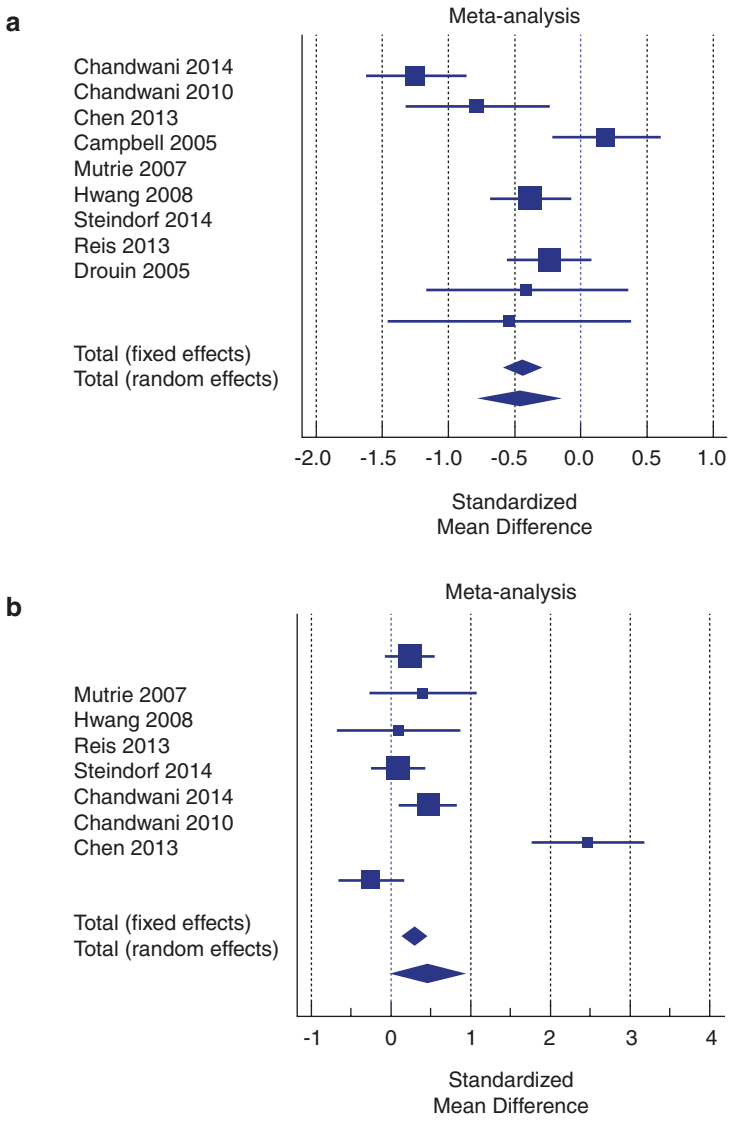

Fig. 9.1 Forest plot from the meta-analysis of Lipsett et al. [27] on fatigue (**a**) and QOL (**b**). Each square represents the standardized mean difference for a study with the horizontal lines representing the associated confidence intervals. Since reduced scores in fatigue represent beneficial effects and increased scores for quality of life, studies on the right of vertical line "0" favor the control group in (**a**) and favor the experimental group in (**b**) and the other way around for studies on the left of the vertical line "0"

exercise group [52]. Pooled analysis of the three studies which explored combined aerobic-resistance exercise, showed a medium-sized and significant reduction in fatigue in favor of the exercise group with no statistical heterogeneity. The low-intensity mind–body exercise showed large-sized but non-significant reduction in fatigue in favor of the exercise groups with large statistical heterogeneity between studies [27].

If reported, most studies included in the meta-analysis by Lipsett et al. were able to show improvements on the functional level in favor for the exercise group. Exemplary for the abovementioned studies one from the aerobic [14] and one from the resistance training area [57] will be presented below.

The aerobic study by US researchers Drouin et al. investigated the effect of a walking intervention for 20–45 min, 3–5 times per week, at 50–70% of measured maximum heart rates during 7 weeks of radiation treatment [14]. Effects were compared against a stretching program. Peak aerobic capacity testing was done showing that the walking group was able to significantly increase aerobic capacity by 6.3%, whereas the stretching group decreased by 4.6% during the intervention period. Serum blood analyses revealed that red blood cell counts, hematocrit, as well as hemoglobin values differed significantly between groups and at the end of the intervention, values were more favorable in exercise group. Results therefore suggest that a moderate-intensity walking intervention is able to maintain erythrocyte levels during radiation treatment of breast cancer compared with the declines observed in stretching control group [14]. A German-based investigative team conducted the BEST study, which investigated the effects of a progressive resistance training (8 machine-based exercises, main muscle groups of upper and lower extremities, 2×/week, 12 repetition maximum, 3 sets) versus group-based relaxation training during radiotherapy. The BEST study reported significant between-group differences favoring the exercise group for maximal isokinetic peak torque in knee flexion and shoulder internal and external rotation, generally showing that strength gain under radiotherapy is possible. Interestingly, subgroup analyses revealed borderline superior strength gain benefits for those patients who had been pretreated with chemotherapy than those without chemotherapy. Further, muscle strength gain in the operated arm was significantly higher than at the non-operated arm. Results indicate that patients with functional restrictions due to breast cancer-related surgery and pretreated with chemotherapy might benefit most from a progressive resistance training program [57].

In line with these findings, another study from Germany published by Kneis et al. in 2018 was especially interested in upper-limb dysfunctions in breast cancer patients being treated with surgery and adjuvant radiotherapy. This study investigated 22 breast cancer patients to determine whether the performed 3×/week exercise intervention incorporating cycling endurance (60–75% HRmax),

handheld vibration exercises, and balance training impacted range of shoulder motion (ROM), isometric handgrip strength, and vibration sense of the affected upper limb compared to a usual care group. Intervention length was 6 weeks during radiotherapy. They observed significantly improved ROM for shoulder abduction (11°) and external rotation (5°) as well as for handgrip strength while controls did not change. Vibration sense worsened in controls while exercises remained stable during the radiotherapy process [25]. The finding underlines the capability of exercise interventions to ameliorate or even prevent radiotherapy-induced functional impairments of the upper extremities in breast cancer patients.

With regard to potential mechanisms of tumor control through exercise, two additional publications should be mentioned coming out of the already above-referenced German BEST study [52, 57]. The analysis of inflammatory parameters done by Schmidt et al. [50] revealed that the 12-week lasting progressive resistance training had a significant effect on IL-6 and the IL-6/IL-1ra ratio, characterized by a manifest increase of those parameters during radiation therapy among the relaxation control group, but no significant change in the resistance training group. The finding suggests that exercise might be able to counteract a significantly increased pro-inflammatory cytokine level after adjuvant radiation therapy in breast cancer patients. Another interesting finding from the BEST study was that the resistance training intervention was able to counteract an activation of the kynurenine pathway that is known to promote cancer progression by inhibiting anti-tumor immune responses and by promoting the motility of cancer cells [59].

To sum up for breast cancer radiation therapy, approximately 10 studies currently show that a variety of exercise interventions during adjuvant breast cancer radiotherapy are safe and seem to be beneficial for various radiotherapy-related side effects like fatigue or shoulder dysfunction resulting in an impaired quality of life [5, 8–10, 13, 22, 35, 38, 52, 57]. Positive effects can be gained if training takes place 2 times per week and incorporates aerobic and/or resistance training components. Evidence for low-intensity mind–body exercise is currently limited.

Besides trials only enrolling breast cancer patients, studies do exist including also other patients than breast. One example and a good transition to the next paragraph is the study done by Mustian et al. [34], investigating breast (n = 27) and prostate cancer (n = 11) patients during radiation therapy. The purpose of their trial was to examine feasibility and efficacy of a 4-week home-based aerobic and progressive resistance exercise intervention compared to a usual care control group not receiving any exercise recommendation. Participants in the exercise intervention showed good adherence and revealed significantly higher quality of life and lower fatigue values post-intervention, indicating that also prostate cancer patients might benefit from an exercise intervention during radiotherapy [34].

Prostate Cancer

Irradiation is one of the ways of permanently stopping tumor growth and curing the disease in early and small localized prostate cancer patients [36]. However, current expert opinion says that there is no certainty whether radiation is better, worse, or just as effective as surgery for early prostate cancer or whether waiting may be just as useful [4]. In case of a high risk of relapse after treatment, radiotherapy is usually combined with androgen deprivation therapy. Locally advanced prostate cancer patients can benefit from radiation again mostly in combination with androgen deprivation therapy. In the situation of radical prostatectomy, adjuvant radiation therapy can be also useful [36]. Radiation therapy should start when the PSA level has dropped as low as possible. The aim is to prevent progression of the disease and the formation of metastases. In case of a PSA rebound after prostatectomy, a so-called salvage radiation therapy can also be considered if the PSA level does not drop or rises again after surgical removal of the prostate. For advanced prostate cancer patients having metastases, radioactive drugs can help to alleviate tumor-related symptoms. Though the evidence is in an experimental developmental stage, this may be particularly true for bone metastases [3].

Most patients tolerate prostate radiation well. However, radiotherapy does not come without side effects. Depending on the situation, acute consequences of irradiation could be, for example, redness of the skin in the irradiation area. With direct prostate radiation, inflammation of the mucous membranes in the bladder and urethra as well as the mucous membrane of the rectum is possible. However, symptoms decline in most patients at the end of treatment. The situation is different with regard to possible long-term or late effects. These include, for example, continence and potency problems, and some patients must also expect long-term damage to the bladder or intestinal mucosa. However, not all men are affected by this after prostate radiation [36].

Evidence of Exercise – Radiation and Prostate Cancer

Historically seen, the research of exercise oncology in prostate cancer patients has a “long lasting” tradition and first studies were conducted more than 20 years ago. Segal et al. [51] published the first study that investigated the effect of an exercise program particularly during radiotherapy in 2009. The goal of the study was to examine the effects of 24 weeks of resistance or aerobic training versus usual care. Outcomes of interest were fatigue, quality of life, physical fitness, body composition, and various blood markers. The Canadian study randomized 121 prostate cancer patients immediately prior to radiotherapy into a usual care, a resistance, or aerobic exercise group. Participants exercised three times per week. In the progressive

resistance training group, they performed 2 sets of 8–12 repetitions of 10 different exercises (machine-based, focusing on large muscle groups of the whole body) at 60–70% of their estimated 1-repetition maximum. Aerobic training participants exercised on a cycle ergometer, treadmill, or elliptical trainer starting at an intensity of 50–60% of their predetermined peak oxygen consumption and gradually increasing intensity over 4 weeks to 70–75%. Duration was also increased with time starting at 15 min until 45 min were reached. Study results showed that the participants were able to follow the prescribed interventions with a median attendance rate of 85.5%. Analyses on the primary outcome of fatigue indicated that both resistance and aerobic exercise benefited in comparison with the usual care control group. In addition, the progressive resistance training program improved QOL, aerobic fitness, upper- and lower-body strength, as well as triglycerides, while preventing an increase in body fat, indicating the importance of resistance training in prostate cancer patients undergoing chemotherapy [51]. Comparable results were also reported by Truong et al. who investigated a 12-week moderate-intensity walking program (3×/week, 60–70% HRmax at least 20 Min) during radical external beam radiation therapy [54].

Following the findings of Segal et al. [51], a study group from Poland asked whether resistance training could induce cytokine responses that could play a role in mediating radiation toxicity by increasing inflammation [20]. Therefore, they set up a study investigating the effect of a supervised resistance training on inflammatory blood markers, as well as on functional capacity, fatigue, and QoL in prostate cancer patients undergoing radiotherapy. Fifty-four men were randomly allocated to a supervised, moderate-intensity resistance exercise or a control group that carried out normal daily physical activity for the duration of radiotherapy treatment. Results revealed that patients in the resistance training group had significant improvement in functional capacity, reduced fatigue, and decreased pro-inflammatory cytokine levels compared to the usual care group [20].

A couple of years prior, a retrospective analysis of a randomized controlled trial from the UK by Kapur et al. had shown comparable results regarding treatment toxicity (according to RTOG/EORTC[1] scales) after external beam radiotherapy. They reported a trend toward less severe acute rectal toxicity following an aerobic walking intervention for 30 min at least three times per week with a statistically significant difference in mean toxicity scores over the 4 weeks of radiotherapy. No effects were found for bladder toxicity [23].

In summary, there are only a few studies available investigating the effect of exercise interventions during radiotherapy in prostate cancer patients. Nevertheless, those studies which do exist showed that exercise is safe and seems to be beneficial for various radiotherapy-affected outcomes like fatigue, quality of life, inflammation, and toxicities in the radiotherapy surrounding areas. It seems to be that positive effects can be gained if training takes place 3 times per week and incorporates aerobic and/or resistance training components.

[1] Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer.

Head and Neck Cancer

Radiotherapy for head and neck tumors is routinely performed following surgery, if the surgery has not been able to remove all tumor tissue, if the safety margins are very tight, or if the tumor has already spread into lymph nodes or other organs. Radiation prior to surgery is less common. Even if a tumor cannot be operated on, radiation is quite often used in combination with chemo- or antibody therapy. Procedures are applied simultaneously as well as consecutively [32].

Head and neck cancer patients experience a wide range of cancer- and treatment-related symptoms including weight loss, muscle wasting, speech and swallowing problems, respiratory impairments, shoulder dysfunction, fatigue, and as a consequence decreased quality of life. The surgical procedure (neck dissection) which is predominantly performed immediately prior to radiotherapy is the leading reason for shoulder dysfunctions and the other mentioned side effects [31]. Therefore, the main question from the exercise oncology perspective is whether radiotherapy interferes with an early-initiated rehabilitative exercise program in this patient group.

Evidence of Exercise – Radiation and Head and Neck Cancer

There are one larger and some smaller trials investigating feasibility and efficacy of exercise intervention in patients with head and neck cancer during radiotherapy. The largest available randomized controlled trial has been published recently with 148 patients having head and neck cancer undergoing chemo-radiotherapy [48]. Results show that there was a significant improvement in the functional capacity, quality of life, and prevention of worsening fatigue for those patients who were randomized to a 5×/week moderate aerobic (15–20 min. Brisk walking) and resistance (6 exercises, 2 sets of 8–15 reps) training program for major muscle groups. The program was conducted hospital-based for 7 weeks during cancer treatment and followed by a 4-week home-based exercise program. The control group received usual care and a standard physical activity recommendation [48].

Another study randomized 60 head and neck cancer patients to either a 12-week lifestyle intervention including a progressive resistance training (2 sets of 8 repetitions at 8–10RM for 10 exercises targeting major muscle groups) during radiotherapy or to a wait-list control group receiving a delayed intervention immediately after radiotherapy had been completed [7]. The primary outcome was body composition measured by BMI and DEXA scans. Results show that regardless of whether patients received the immediate or delayed intervention, they benefitted with respect to body composition, fitness, quality of life, depression, and nutritional scores. However, patients randomized to the delayed intervention group showed improved intervention adherence, indicating that this period might be more convenient for head and neck cancer patients to follow an exercise program [7].

Sandmael et al. [49] followed a comparable research question, and the study results were comparable with those of Capozzi. Forty-one patients were either

randomized to a combined exercise and nutrition intervention 2×/week during radiotherapy (hospital-based) or to a wait-list control group starting with the intervention after radiotherapy completion (rehab center-based) within this feasibility trial. Interventions consisted of progressive resistance training (2 lower body exercises and 2 upper body exercises; 3–4 sets at 6–12 repetitions maximum) and oral nutritional supplements. Results show that the adherence (attendance rate) to the resistance training intervention was quite high with 81% during radiotherapy but even higher for the group that started to train after the end of radiotherapy (94%). However, this comparison has to be interpreted with caution since the intervention length was twice as long during radiotherapy (6 weeks) as after radiotherapy (3 weeks). Furthermore, the intervention after radiotherapy was done in a rehab center where the patients stayed overnight during weekdays resulting in the very unlikely event that a patient would miss a training session due to other responsibilities in daily life (e.g., other appointments, interfering daily routines). Beside feasibility, this study documented no intervention effect on muscle mass [49].

Following the same idea of Sandamael et al. and Capozzi et al., another research group (Londbro et al.) asked the question about feasibility and effectiveness of an early-initiated (immediately after radiotherapy) 12-week progressive resistance training program versus a delayed initiation of the same program. Progressive resistance training consisted of seven machine-based exercises targeting major muscle groups. Patients received professional instruction during two to three initial sessions and performed 2–3 sets of 8–15 repetition maximum for each exercise. All subsequent training sessions were unsupervised. In total, 41 patients were randomized and analyzed. Results show that lean body mass could be significantly increased by 4.3% during the first 12 weeks in the early-initiated resistance training group in comparison to the wait-list group. However, the same was true (increased lean body mass by 4.2%) for the wait-list group after the end of the delayed intervention period. Comparable results were found for functional performance and quality of life, indicating progressive resistance training was beneficial for head and neck patients following radiotherapy, irrespective of an early-initiated or delayed intervention start [28].

Beside the mentioned studies, various other small trials with a sample size between 12 and 20 participants exist focusing different questions in the field of exercise oncology and radiotherapy in patients with head and neck cancer [46, 58]. They add interesting topics to the field. For example, the pilot randomized controlled trial by Grote et al. [17] focused on the feasibility of machine-based progressive resistance training (3×/week, 3 exercises, 3 sets 8–12 repetition maximum) in cachectic head and neck cancer patients during radiotherapy. Ten patients were randomized to the intervention and ten to usual care. Assessments were done before radiotherapy, after 7 weeks of radiotherapy and 8 weeks after the end of radiotherapy. Results showed safety of the intervention in this vulnerable patient group and improvements of weight loading for leg press (+19.0%), chest press (+29.8%), and latissimus pull-down (+22.8%). However, patient-reported outcomes showed no significant changes over the course of the study, but a trend for a better development of general fatigue and quality of life for the intervention group. Nevertheless,

the authors concluded that exercise adherence was excellent, despite the recognized advanced tumor stage, the cachectic situation, and the burdensome treatment in this patient group [17].

In summary, there are a few studies in the field of head and neck cancer investigating the effects of exercise interventions during adjuvant radiotherapy. All studies reported no adverse events due to the exercise interventions supporting the conclusion that exercise is safe for head and neck cancer patients during radiotherapy. Since head and neck cancer patients are at risk for muscle wasting and cachexia, resistance training is the corner stone in nearly all of the currently available studies. Positive effects on various outcomes (muscle strength, body composition, fatigue, depression, quality of life) can be gained if training takes place 2–3 times per week and incorporates resistance training components with an intensity level aiming for muscle hypertrophy (8–12 reps at 60–80% of 1 repetition maximum).

Other Cancers

For cancers other than breast, prostate, and head and neck, there are only single studies available investigating the effect of an exercise intervention during radiotherapy treatment.

Despite the fact that a lung cancer diagnosis is one of the most frequent cancer types worldwide, the evidence in the area of exercise oncology is limited. However, a recent but small (n = 15) randomized trial conducted in the Netherlands was able to show that an individually supervised, structured, moderate-to-high intensity cycle ergometer training program immediately before radiotherapy in patients undergoing concomitant chemo-radiotherapy was feasible (attendance rate 90.0%) and locally advanced lung cancer patients were able to follow the exercise prescription in 88.1%. of all sessions. Exercise training consisted of 20 min moderate-to-high intensity aerobic interval training 5 times per week for 7 weeks prior to radiotherapy. With regard to efficacy, no significant differences were observed within or between groups, which might be caused by small sample size [15].

A Canadian single-arm feasibility study focusing on 18 rectal cancer patients during and after neo-adjuvant chemo-radiotherapy showed that patients were able to attend 83% of their supervised aerobic exercise sessions (3×/week, 40–60% of estimated VO2 reserve, up to 50-min/session) during the 6-week intervention period. They were also able to perform 222 min per week of additional unsupervised exercise. Furthermore, no serious adverse events occurred underlining the finding that exercise is also feasible during chemo-radiotherapy in this population [33].

A very interesting case report by Hansen et al. [18] describes the feasibility and effectiveness an exercise intervention in a patient with a glioblastoma. The 54-year-old man followed a 1:1 supervised individually tailored 6-week exercise intervention (incorporating endurance, resistance, and balance exercises) program during radiation treatment. Brain surgery had been successfully done 42 days before. Attendance rate was 100% and the patient improved in aerobic and strength

performance, standing balance as well as walking ability over the course of brain irradiation. Furthermore, various quality-of-life domains were positively affected by the intervention program. Even though this is just a single case, findings are promising that exercise has the ability to maintain or improve functional performance and quality of life even during intense radiotherapy treatment of the brain. Findings also imply that patients with glioblastoma are able and may be willing to participate in exercise programs during radiotherapy [18].

In summary, the area outside the entities of breast, prostate and head and neck cancer patients is completely understudied from the perspective of exercise oncology and radiotherapy. Those studies which are available suggest that exercise is safe, feasible, and maybe beneficial in the group of rectal and lung cancer patients.

Evidence for Exercise Oncology During Palliative Radiotherapy

Radiotherapy plays a vital part in the treatment of advanced cancer patients. A particular interest from the exercise oncology perspective can be identified in cases of bone metastases since patients with (instable) bone metastasis are often treated orthopedically, receive corsets, and/or get the order to restrict physical activities/movements to a minimum (sometimes bed rest) to prevent pathological fractures [41]. Interestingly, those procedures have not shown any benefits for those who are affected and mostly further decrease in patients` quality of life. A study, retrospectively looking in particular at the incidence rates of pathological fractures after radiotherapy in 915 patients with and without orthopedic corsets, revealed that a corset supply in patients with spinal metastases does not significantly prevent pathological fractures compared to those patients who were not wearing a corset [41]. Regarding radiotherapy procedures, bone metastases are typically treated with 10 sessions of external radiation. Radiation therapy can help to stabilize the affected bone region and can relieve metastasis-caused pain relatively quickly.

Given these findings and being aware of the findings in the area of exercise oncology, one might think that a muscular stabilization of the bone lesion area during and after palliative radiotherapy is a suitable and beneficial approach for affected patients. However, there are only two studies that have been published in this field and both are from the same German research group around Rief and colleagues.

The first study compared the effects of resistance training program versus passive physical therapy during radiation therapy in patients with spinal bone metastases classified as stable. Sixty patients were equally randomized either to a resistance training program or to a physical therapy group receiving breathing exercise. Resistance training consisted of three strength exercises (four point leg and arm raise, gluteus arch/bridge, lifting pelvis in supine position) addressing the supporting muscles of the spinal column. Repetitions were defined on an individual level with the goal to repeat each exercise 4–8 times per set with the goal of performing 2 sets. While performing the exercise, patients were encouraged to stay a couple of seconds in a holding position under muscular tension resulting in a large isometric resistance training component [42]. The exercise program was done in the first

2 weeks five times a week in a supervised setting (during hospital stay for bone metastasis radiation) and followed by a 6-month home-based training period where the patients were encouraged to train thrice weekly.

First and most importantly, study results demonstrate that the exercise intervention was feasible in about 83% of the patients and no adverse events occurred during the 6-week intervention time [43]. Furthermore patients in the exercise group were able to achieve a significant reduction in pain sensation in comparison with the control group. It could also be shown that functional capacity improved, fatigue reduced, and thereby enhanced quality of life was achieved in the exercise group [39, 43, 45]. With great interest from a radio oncology point of view was the finding that patients of the resistance training group had better bone density results in the area of the irradiated bone structures, suggesting a preventive capability with regard to pathologic fractures [44]. The suggestion might be supported by the observation that no local bone progression was detected in the exercise group after a median follow-up of 10 months [40].

Given the findings of the abovementioned trial, the group of Rief and others conducted a second, exploratory, randomized trial study to investigate safety/feasibility of isometric paravertebral muscle training in patients with spinal metastases classified as unstable [55]. The study design, length, and procedure were comparable to the first trial (see above). However, exercise intervention was modified to increase impact on paravertebral muscles (see Fig. 9.2), and patients in the control group received an audio-guided progressive muscle relaxation program.

Analyses revealed that there were no adverse events either in the resistance or relaxation program. More than 80% of the planned sessions were completed by 55%

Fig. 9.2 Exercises of the DISPO-II trial [55]

(n = 16/29) of the patients in the relaxation group and 67% (n = 18/27) in resistance training group during radiotherapy. Post-radiotherapy adherence data for home-based training showed comparable results. Different from the study in patients with stable bone metastases, there were no differences in pain scores, use of analgesic agents, or bone density between groups. Further, no difference in quality-of-life data was observed. Pathological fracture rates were also not statistically different between groups (Exercise: n = 1 vs. Relaxation: n = 3) after 3 months. Nevertheless, even not showing the same beneficial results like in patients with stable bone metastases the authors concluded that anisometric paravertebral muscle training in patients with high-risk unstable spinal metastases is potentially feasible. However, more research is needed.

Besides those two studies in the special area of exercise interventions in patients with bone metastases undergoing palliative radiotherapy, a few other data show that exercise interventions are possible in advanced cancer patients. The US study conducted by Cheville et al., for example, showed that an individualized and structured physical therapy program (incorporating strength exercises for low/upper extremities and trunk) was feasible in patients undergoing outpatient radiation therapy for advanced cancer. Data analysis of 103 participants (major entities: GI, Head and Neck, Lung, Brain) undergoing radiation therapy revealed that physiotherapy sessions (which were part of a multidisciplinary intervention) attendance was 89.3%. In addition, physical well-being scores were improved at week 4 in the intervention group and significantly declined in the control group, suggesting a beneficial effect of the intervention. However, group differences were no longer detectable during follow-up assessments, and therefore sustainability was established [11]. A comparable study also followed the idea of a multidisciplinary intervention approach and incorporated an exercise intervention as a central element. This latter study showed that even cancer patients of elderly age can benefit from such programs during radiotherapy [26]. Another case study published by Hartland et al. showed that exercise interventions are possible even when the patient seems to be extremely limited by the disease/metastasis itself or due to the intense treatment [19]. A 57-year-old male who exercised regularly and continued to exercise during stereotactic ablative radiotherapy treatment for a renal cell metastasis in his left lung was able to follow an exercise program that included 5 × 60-min moderate-intensity aerobic exercise sessions and 3 × 45-min resistance exercise sessions per week for 12 weeks post treatment (adherence rate: 98%). Minimal changes were observed in fitness and patient-reported outcome values, demonstrating that exercise may be feasible for patients undergoing radiotherapy for the treatment of lung metastasis and may improve relevant outcomes [19].

Exercise Interventions and Radiotherapy: Basic Science Perspectives

Baring the abovementioned clinical trial evidence, the relevance of adding exercise interventions to radiation as an adjunct treatment approach is also supported by emerging evidence from preclinical studies. Findings in basic science research world indicate that exercise interventions might be able to regulate intratumoral

vascular maturity and perfusion, hypoxia, and metabolism and to augment the antitumor immune response [1]. Such modulations of the tumor milieu might also enhance responses to anticancer treatment regimens, and there is also a vital rationale that this could be true for radiotherapy.

Efficacy of radiotherapy is based on sufficient oxygen delivery in the tumors and the surrounding milieu to generate radiation-induced reactive oxidative species, which facilitates the death of tumor cells. This means radiotherapy works poorly in hypoxic tumors [12]. It is well known that exercise affects the cardiovascular system through increased blood circulation and oxygen delivery to peripheral tissues. This led consequently to the idea that exercise could support the anticancer effect of radiotherapy by increasing intratumoral blood perfusion. A study using a prostate tumor model by McCullough et al. showed that treadmill running in rodents was able to increase intratumoral blood perfusion and relieved intratumoral hypoxia. Furthermore, they demonstrated that blood perfusion of the remaining prostate not affected by the tumor remained unchanged during exercise [29]. These findings are counterintuitive since exercise-driven blood flow regulation is leading to direct the blood to the "active" organs, while limiting blood flow to "inactive" organs during exercise. However, several other basic science studies have shown an upregulated intratumoral blood perfusion following an exercise intervention [16, 29, 30]. Interestingly, there might be supportive study results for these findings in patients with locally advanced rectal cancer undergoing a preoperative radio-chemotherapy in combination with 6-week supervised aerobic exercise (3×/week) weekly sessions compared to a usual care group [56]. The findings support the assumption of improved intratumoral blood perfusion. More specifically, all patients in the aerobic exercise group experienced a significant tumor downstaging in response to neo-adjuvant chemo-radiotherapy compared with 61% in the control group.

Referring back to the basic science field revealed also very interesting findings from studies focusing on the interaction effect of radiotherapy and exercise. A recently published study done by Sahnoune et al. [47] investigated the development of Fischer rats which were brain-irradiated with a fractionated dose of 4 Gy × 5 days at an age of 31 days, which were then trained and tested at 6, 9, and 12 months post-radiation. Analyses of brain images and reaction time testing revealed that radiation caused early and lasting impairments in reaction time and correct response to the task. It also created a stunting of growth and changes in brain volume and diffusion. When Fischer rats were exercising after irradiation, various reaction time outcomes improved, the stunting of brain size was mitigated, and increased brain fiber numbers were seen in comparison with sedentary rats. Therefore, data suggest that exercise may be useful at improving cognitive outcome following brain radiation [47].

Conclusion and Practical Recommendations

Current findings suggest that exercise is feasible and beneficial during radiotherapy for the management of common side effects like fatigue or reduced functioning, resulting in an insufficient quality of life of the treated patients. Most evidence exists

for early-stage breast cancer patients undergoing radiotherapy followed by head and neck and prostate cancer patients. So far, based on the current literature, it can be suggested that supervised exercise interventions seem to be more effective in alleviating symptoms, and supervision seems to be mandatory in high-risk situations like exercising with patients having unstable bone metastasis undergoing palliative radiotherapy. Aerobic as well as resistance exercise seems to be promising for patients undergoing radiotherapy. However, from a practical perspective, feasibility of exercise interventions in real life is sometimes impeded by recommendations provided by radiotherapy staff. For example, since radiotherapy markers on the skin usually react sensitively to sweating or showers, staff advise patients to avoid such situation, which definitely impacts the willingness to exercise. Therefore, radiotherapists should be asked to draw the markers with waterproof pencils or to cover them with clear plaster.

In general, few exercise oncology studies have chosen the setting of radiation treatment as the field of interest. Therefore, generally more research is needed in the field of exercise oncology and radiation. This is of particular relevance, since the radiotherapy period might be a suitable treatment window for professional (hospital/cancer center-based) exercise oncology support. Why? Curative radiotherapy is often well tolerated by patients, and it is mostly applied a few weeks after surgery and/or chemotherapy (both known to cause a variety of side effects). Since patients are coming in on a daily basis, barriers to participate in a local exercise program prior or after the radiotherapy should be very low. Therefore, the radiotherapy treatment period might be an important setting to implement structured exercise oncology support for cancer patients. Future studies should aim at identifying effective exercise prescription parameters according to the FITT (frequency, intensity, time/duration, and type) in line with the recently published round table results on exercise oncology [6]. In addition, efforts should be made to translate basic science knowledge into practice changing studies by setting up comprehensive research programs with the goal (1) to elucidate the interaction between exercise and radiotherapy treatment on tumor and tumor milieu response and (2) to test potential mechanisms in clinical studies using the more and more developing neo-adjuvant treatment as a setting where tumor tissue is available.

Translating the current evidence into a FITT prescription would lead to the recommendation for patients undergoing curative radiotherapy to follow an exercise intervention consisting of aerobic and resistance training elements for 2–3×/week each, with a moderate intensity (aerobic training, HRmax 60–70%; resistance training, 60–80% of one-repetition maximum), for at least 20–30 min for aerobic activity or 2 sets of 6–8 larger muscle groups for resistance exercise. Patients undergoing palliative radiotherapy should only follow supervised and highly individualized programs with a 1:1 support in patients having unstable bone metastases.

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Chapter 10
Effects of Exercise on Cancer Treatment Completion and Efficacy

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Cancer is a complex disease that has many different treatment options including surgery, chemotherapy, radiation therapy, hormone therapy, and immunotherapy. In many cases, individuals will receive a combination of these treatments either concurrently or sequentially. The effectiveness of these treatments depends largely on their substantive completion which, unfortunately, is not always optimal. Cancer treatments are often reduced, interrupted, or discontinued because of substantial toxicities and/or side effects including hematologic toxicities, neurotoxicity, cardiotoxicity, pain, and fatigue. Interventions to manage toxicities and improve treatment completion would be beneficial and could ultimately lead to better disease control and survival. Evidence from multiple clinical exercise intervention trials has demonstrated that exercise is effective at mitigating some cancer treatment-related side effects and, therefore, may improve treatment completion rates (Fig. 10.1). The first purpose of this chapter is to examine the potential impact of exercise during cancer treatments on the completion rates of various cancer treatment modalities.

Even if completed, however, cancer treatments are not always effective. Some individuals achieve substantial benefit, some modest benefit, and some no benefit at all. Interventions to improve the efficacy of cancer treatments would also be highly beneficial to patients. Emerging evidence from preclinical studies supports several biologically plausible mechanisms via which exercise may improve the efficacy of cancer therapies or exhibit direct effects on tumor growth and metastases (Fig. 10.1). The second purpose of this chapter is to examine the effects of exercise during cancer treatments on treatment response and disease outcomes.

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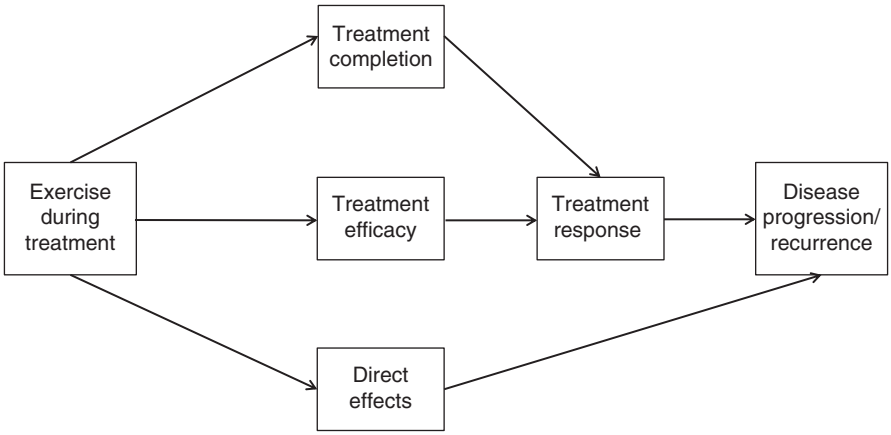

Fig. 10.1 Proposed clinical pathways of exercise during cancer treatment on treatment and disease outcomes

Treatment Completion

Chemotherapy

The effectiveness of chemotherapy is dose dependent, and any reductions and/or delays can undermine treatment efficacy [1, 2]. Chemotherapy dose intensity represents the amount of drug delivered per unit of time and is expressed in mg/m^2/week [3]. Although clinical thresholds may vary by cancer type, disease stage, and treatment regimen, evidence from clinical trials in breast cancer and lymphoma suggests that maintenance of ≥85% of the planned chemotherapy dose intensity is associated with better outcomes [4–6]. Chemotherapy can cause substantial toxicities and side effects that result in modifications to the planned regimen in the form of dose reductions or dose delays.

In clinical practice, adverse effects of cancer treatments are assessed using the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE defines an adverse event as either an unfavorable or an unintentional sign (e.g., abnormal laboratory finding or abnormal finding on examination) or symptom (e.g., fatigue, pain, and neuropathy). Furthermore, symptoms are evaluated for their degree of interference with activities of daily living. Consequently, the decision to modify the planned chemotherapy regimen is based on both clinical and patient-reported factors. The severity of a sign or symptom is graded from 1 (mild) to 5 (death) with grades 3 (severe) or 4 (life-threatening) most often being an indication to modify the planned chemotherapy dosage. Exercise has been identified as an effective strategy for managing some toxicities and side effects and improving quality of life during adjuvant chemotherapy in several cancer patient groups [7]; consequently, it is possible that exercise may also improve adherence to chemotherapy treatments.

Bland et al. [8] recently conducted a systematic review examining the effects of exercise on chemotherapy completion rates. In their review, they identified seven randomized controlled trials with chemotherapy completion as an outcome, two of which reported significant findings [9, 10]. In the START trial [9], women with early stage breast cancer undergoing adjuvant chemotherapy were randomized to either supervised aerobic exercise training, supervised resistance exercise training, or usual care. Resistance exercise training was statistically superior to usual care for improving chemotherapy completion rate (89.8% in the resistance training group vs. 84.1% in the usual care group; $p = 0.033$). Aerobic exercise training was numerically superior to usual care (87.4%). Additional nonsignificant between-group differences were observed for the number of patients receiving ≥85% of their planned chemotherapy dose (65.9% in the usual care group vs. 78.0% in the resistance training group and 74.4% in the aerobic training group). Moreover, the usual care group received more granulocyte-colony stimulating factor than the resistance exercise training group which possibly worked against an even larger effect. In ancillary analyses, exercise adherence in both the aerobic and resistance training groups was associated with receiving a higher dose of planned chemotherapy. Moreover, improvements in lean body mass in the resistance exercise training group, compared to the usual care group, were associated with a higher percentage of patients completing ≥85% of their planned chemotherapy dose. Reasons for dose reductions were not reported in the START trial.

In the PACES trial [10], women with early stage breast cancer were randomly assigned to three groups including a low-intensity home-based exercise program, a supervised moderate-to-high-intensity combined resistance and aerobic exercise program, or usual care. Significantly fewer women in the supervised combined resistance and aerobic exercise program required chemotherapy dose modifications (12%) compared to both the home-based exercise program (34%) and usual care (34%). Moreover, the average dose reductions were 10% in both exercise programs compared to 25% in the usual care group. The main reasons for dose adjustment across all groups were neuropathies (31%), myelosuppression (11%), febrile neutropenia (11%), and nausea and vomiting (11%). Statistical differences between the groups were not reported; however, the rates of dose reductions for febrile neutropenia were numerically higher in the usual care group ($n = 6$) compared to both the low-intensity exercise group ($n = 0$) and the moderate-to-high-intensity exercise group ($n = 2$).

It is important to note that in all the trials reviewed by Bland et al. [8], chemotherapy completion was a secondary or an exploratory outcome. Thus, these trials were not designed to determine if exercise may improve chemotherapy completion rates. Nevertheless, this preliminary evidence is encouraging, and as Bland et al. [8] pointed out, more research into the mechanisms through which exercise training may improve chemotherapy completion rates is needed. Moreover, Sanft et al. are currently conducting the first lifestyle intervention with chemotherapy completion as the primary outcome [11]. The LEANER study is examining the effects of a healthy diet and exercise, compared to usual care, on chemotherapy completion rate in women with early stage breast cancer.

Although limited, studies examining the predictors of treatment toxicity and chemotherapy completion rates in large clinical trials have identified non-modifiable (e.g., age and disease stage) and modifiable (e.g., body mass index, body surface area, performance status, and the presence of comorbidities) variables in some cancer types [12–15]. Researchers in the field of exercise oncology are especially interested in identifying and studying modifiable factors that may be positively influenced by exercise. As previously noted by Bland et al. [8], low muscle mass and functional fitness are emerging as potentially important determinants of chemotherapy treatment toxicity and/or treatment completion rates [16, 17].

Mechanisms of Exercise-Mediated Improvements in Chemotherapy Toxicity and Completion

Sarcopenia (low skeletal muscle mass) and sarcopenic obesity (low skeletal muscle mass and excessive adipose tissue) have been identified as determinants of chemotherapy treatment toxicity across several cancer types and chemotherapy agents [16]. Most chemotherapy regimens are prescribed according to total body surface area. Body surface area is a function of height and weight and does not account for individual differences in body composition. Pharmacokinetics (i.e., drug distribution and metabolism) are driven by blood flow and perfusion and occur in lean tissue. Thus, in theory, the volume through which a drug can be distributed is reduced in someone with low muscle mass, thereby increasing their risk of developing dose-limiting toxicities in the blood (i.e., a higher plasma concentration of the drug) and in highly perfused organs such as the liver, kidneys, and heart.

Christensen et al. recently described cancer drug distribution in untrained vs. trained individuals [18]. Their model suggests that when two individuals with the same body surface area receive the same dose of chemotherapy, the drug will be distributed to a smaller area in the untrained individual (low muscle mass, high fat mass) compared to the trained individual (high muscle mass, low fat mass), making the untrained individual more likely to experience treatment toxicities. In addition to sarcopenia (and sarcopenic obesity), poor functional fitness has recently been associated with completing fewer cycles of chemotherapy in advanced non-small cell lung cancer [17]. Treatment toxicities and reasons for dose modifications were not reported. There is considerable overlap between sarcopenia and poor functional fitness, and muscle mass and strength are key components. Although muscle mass, muscle strength, and physical functioning are interrelated, it is unclear which of these should be the target of exercise interventions designed to improve treatment toxicity and completion for cancer patients. Interestingly, resistance training in the START trial and combined resistance and aerobic exercise training in the PACES trial were superior to usual care at improving chemotherapy completion rates. Moreover, in the START trial, improvements in lean body mass were associated with chemotherapy completion rates ≥85%. It is unclear if this association was mediated by reductions in treatment toxicity as reasons for treatment modifications

were not closely tracked in the START trial; however, it is unlikely that other factors would have strongly influenced the decision to modify treatments.

In addition to the chronic effects of exercise training on muscle mass, Christensen et al. [18] noted that during an acute bout of exercise, blood perfusion in the skeletal muscle increases substantially which could add to the volume through which chemotherapy drugs may be distributed, thereby reducing toxicity in the blood and other organs. This mechanism suggests that exercise training involving large muscle groups during chemotherapy infusion may be the most effective at mediating treatment toxicities. To date, two pilot studies have reported the feasibility and safety of aerobic exercise during chemotherapy infusion [19, 20]. Kirkham et al. [21] are currently examining the impact of a single bout of exercise 24 hours prior to chemotherapy infusion on treatment toxicity and treatment response in women with breast cancer receiving anthracycline [21]. Their rationale is based on preclinical evidence of a cardioprotective effect and a pilot randomized controlled trial demonstrating the feasibility of the exercise intervention [22–25]. Moreover, the same group is studying the effects of caloric restriction and a moderate-intensity exercise session during chemotherapy infusion on tumor response in breast cancer patients with metastatic disease [26].

More recently, Christensen et al. [18] have suggested that exercise may reduce chemotherapy treatment toxicities via improvements in immune function. Acutely, exercise training causes an increase in circulating immune cells. Moreover, it has been suggested that the acute release of immune cells stimulated by exercise may provide a feedback response to the bone marrow to produce new immune cells further helping the body's defense mechanisms [18]. Exercise-mediated improvements in immune function could reduce hematologic toxicities which are a common reason for dose modifications across different cancer types and chemotherapy regimens. Several studies have examined the impact of exercise on immune function in cancer patients during (and after)chemotherapy and have found mixed results: some findings have indicated no change and others have indicated improvements in immune function parameters [27]. Nonetheless, these early results suggest the possibility of immune function mediated improvements in chemotherapy completion rates in cancer patients engaging in an exercise training program.

Radiation Therapy

Similar to chemotherapy, the effectiveness of external beam radiation therapy is dependent on receiving the treatments as planned. Although limited, research from large clinical studies suggests that local disease control and overall survival (OS) decrease as the total time to complete treatment increases. In head and neck cancer and cervical cancer, each day of treatment interruption has been associated with approximately a 1% reduction in local control [28, 29]. Moreover, delays exceeding 5 days (i.e., 1 week as radiation therapy is normally delivered on weekdays only)

have been associated with reduced local control and survival in cervical squamous cell carcinoma [30]. In general, adherence to the planned number of radiation fractions is high; nevertheless, toxicities of grade 3 or 4 (e.g., fatigue, dermatologic toxicities, and hematologic toxicities) can cause a reduction, delay, or discontinuation of radiation therapy. The severity of the side effects, and consequently adherence to radiation therapy, may vary according to cancer type, treatment timing, treatment regimen, and individual factors. To date, very few exercise intervention trials have been conducted during radiation therapy, and none have reported on radiation therapy completion rates [31–35].

A recent systematic review and meta-analysis examining the effects of exercise interventions during adjuvant radiation therapy for breast cancer found that supervised combined aerobic and resistance training improves fatigue [33]. Moreover, Rogers et al. have demonstrated that resistance training during radiation therapy for head and neck cancer improves fatigue and functional fitness compared to no exercise [31]. Whether exercise-mediated improvements in side effects from radiation therapy translate into improvements in treatment adherence remains unknown. One ongoing phase II trial that will report on this issue is the EXERT trial [36], a randomized controlled trial comparing high-intensity aerobic exercise to usual care in rectal cancer patients receiving neoadjuvant combined chemotherapy and radiation therapy. Treatment toxicity and treatment completion are prespecified as exploratory outcomes in the EXERT trial.

Hormone Therapy

Hormone therapy is commonly prescribed to treat hormone-dependent breast and prostate cancers. These treatments significantly improve long-term survival; however, adverse effects including hot flashes, arthralgia, fatigue, changes in mood, and bone loss often result in suboptimal treatment adherence. Reviews of both clinical trials and clinical practice settings have found that up to 50% of breast cancer survivors either on tamoxifen or an aromatase inhibitor (AI) do not take their drug as prescribed or discontinue therapy altogether [37]. Moreover, treatment side effects (e.g., menopausal symptoms and arthralgia) are strongly associated with adherence to the treatments [37]. Very few studies have examined the effects of exercise in breast cancer patients on hormone therapy. In the HOPE trial, Irwin et al. [38] examined the effects of a 1-year exercise program consisting of two supervised resistance training sessions per week and 150 minutes per week of unsupervised aerobic exercise, compared to usual care, on the severity of arthralgia in women receiving AIs. Joint pain severity and interference improved in the exercise group; however, there was no statistically significant difference between the exercise group (80%) and the usual care group (76%) for adherence to daily AI therapy. The HOPE trial was not designed to examine AI treatment adherence; therefore, studies are needed to directly examine this question.

To date, numerous studies have examined the effects of exercise in men with prostate cancer receiving androgen deprivation therapy (ADT); however, none have

reported on adherence to ADT. Although clinical trials have reported a low percentage of grade 3 and grade 4 toxicities caused by ADT [39, 40], treatment side effects including muscle loss, fatigue, changes in mood, sexual dysfunction, and weight gain appear to influence the receipt of long-course (vs. short-course) ADT in practice [41]. The side effects associated with ADT can negatively impact the quality of life of men with prostate cancer [40] which may influence their decision to continue with treatment. Moreover, it is possible that some of the risks associated with ADT (e.g., cardiovascular events) may influence a physician's recommendation to initiate (and continue) with ADT based on comorbidities and age [41]. The effects of exercise on ADT adherence are an important question that should be addressed in future exercise trials.

Immunotherapy

Immunotherapy is emerging as a promising treatment for cancer that has been associated with improved disease outcomes in metastatic melanoma, non-small cell lung cancer, head and neck squamous cell cancer, renal cell cancer, bladder cancer, colorectal cancer, and hematologic cancers [42]. Many different types of immunotherapy are used to treat cancer including monoclonal antibodies, immune checkpoint inhibitors, conjugated monoclonal antibodies, and nonspecific immunotherapy. The most common grade 3 and 4 toxicities associated with immunotherapy are driven by autoimmunity and include skin reactions (rash, itching), fatigue, pneumonitis, diarrhea, and loss of appetite [42]. The effects of exercise on side effects from immunotherapy and ability to complete these treatments are unknown, but they are important research questions as exercise may be beneficial but could also be harmful (i.e., worsen symptoms).

Treatment Efficacy

The ability of cancer treatments to eradicate cancer cells is of uttermost importance to clinicians and patients. The effectiveness of cancer treatments will vary based on cancer type, stage at diagnosis, tumor biology, as well as individual factors. The 5-year relative survival rate for all cancers is 69%, and survival is highest for prostate cancer (99%) and lowest for pancreatic cancer (10%) when all stages of the disease are combined [43]. It has been proposed that exercise training may enhance the efficacy of standard cancer treatments including chemotherapy, radiation therapy, and immunotherapy through a series of systemic and local (i.e., tumor microenvironment) physiological adaptations which ultimately could improve the delivery and cytotoxic effect of cancer treatment.

The potential impact of exercise on cancer treatment response is complex and is dependent on whether exercise may have direct effects on tumor growth and/or metastases (Fig. 10.2). Under a scenario where exercise is known to have its own

			Cancer treatment efficacy (ES = 4)		
			Reduced	**Unchanged**	**Enhanced**
Exercise direct effect	**Negative**	(ES = –4)	Subtractive (ES = 0–3) Antagonistic (ES < 0)	Neutralizing (ES = 4)	Additive (ES > 4)
	Neutral	(ES = 0)	Antagonistic (ES < 4)	Neutralizing (ES = 4)	Additive (ES > 4)
	Positive	(ES = 4)	Antagonistic (ES < 4)	Redundant (ES = 4)	Additive (ES = 5–8) Synergistic (ES > 8)

Fig. 10.2 Possible effects of exercise during cancer treatment on treatment efficacy. Notes: ES = hypothetical effect size

positive direct effects on tumor growth or metastases (i.e., exercise is an active single agent), exercise may interfere with cancer treatment efficacy (i.e., an antagonistic effect), have no additional effect on treatment efficacy (i.e., a redundant effect), or enhance treatment outcomes in a manner consistent with the known independent effects (i.e., an additive effect) or in a manner that is larger than the known independent effects (i.e., a synergistic effect). Under a scenario where exercise is known to have no direct effects on tumor growth or metastases, exercise may interfere with cancer treatment efficacy (i.e., an antagonistic effect), have no effect on treatment efficacy (i.e., a neutralizing effect), or enhance treatment efficacy (i.e., a sensitizing effect). Finally, under a scenario where exercise is known to actually have a *negative* direct effect on tumor growth or metastases (i.e., exercise makes the cancer grow or spread more quickly), exercise may reduce treatment outcomes in a manner consistent with the known independent effects (i.e., a subtractive effect) or interfere with treatment efficacy in a manner that is larger than the known independent effects (i.e., an antagonistic effect), have no effect on treatment efficacy (i.e., an inert effect), or enhance treatment efficacy (i.e., a sensitizing effect).

Chemotherapy

Several characteristics of the tumor microenvironment (TME) lead to chemotherapy resistance. Most notably, the TME is characterized by abnormal vascularization and poor blood perfusion which impairs the delivery of anticancer drugs. Exercise training stimulates angiogenesis and improves blood flow (via NO- and VEGF-mediated pathways) which has broad-reaching effects (not limited to the skeletal muscle) and therefore has the potential to induce favorable changes in the TME. Evidence from preclinical studies suggests that repeated bouts of aerobic exercise improve TME vascularization and normalization as demonstrated by a reduction in tumor hypoxia [44, 45]. However, studies examining whether or not these changes translate into therapeutic benefit are mixed [46–49]. Jones et al. [46] randomly assigned

female mice injected with MDA-MB-231 breast carcinoma cells to doxorubicin only, moderate-intensity aerobic exercise only, doxorubicin plus moderate-intensity aerobic exercise, or control. Survival rate significantly improved in the doxorubicin only and the doxorubicin plus exercise groups, compared to the control group. Additionally, exercise only had no effect, compared to control (i.e., neutral effect), on survival rates. Interestingly, doxorubicin plus exercise not only had no additional benefit on survival compared to doxorubicin only but also made the outcomes worse (i.e., a possible antagonistic effect).

Sturgeon et al. [47] examined the effects of low-intensity aerobic exercise on doxorubicin efficacy in mice injected with B16F10 melanoma cells in a four-arm randomized controlled trial (i.e., doxorubicin only, exercise only, doxorubicin plus exercise, control). Tumor volume significantly decreased in both the doxorubicin only and doxorubicin plus exercise groups, compared to the control group with even larger effects observed for the doxorubicin plus exercise group, compared to the doxorubicin only group. Interestingly, exercise alone appeared to have a negative effect, compared to control, on tumor volume; however, doxorubicin plus exercise had a sensitizing effect. Betof et al. [48] randomly assigned female mice injected with breast cancer cells to cyclophosphamide only, aerobic exercise only, cyclophosphamide plus aerobic exercise, or control. Tumor growth was significantly reduced in the cyclophosphamide plus aerobic exercise group, compared to all other groups. Additionally, cyclophosphamide only and exercise only both significantly reduced tumor growth compared to the control group. Moreover, the magnitude of the individual effects of cyclophosphamide and exercise were approximately the same (around 200 mm^3 tumor size reduction), and the magnitude of the effect of cyclophosphamide plus exercise has approximately doubled this effect (around 400 mm^3 tumor size reduction), suggesting that the exercise did not interact with the treatment but rather had an additive effect. More recently, Shadler et al. [49] found that doxorubicin plus moderate-intensity exercise in mice with B16F10 melanoma tumors and gemcitabine plus moderate-intensity exercise in mice with PDAC-4662 pancreatic cancer significantly reduced tumor growth, compared to doxorubicin alone or gemcitabine alone. Exercise only promoted tumor growth in B16F10 melanoma cancer and had no effect on tumor growth in PDAC-4662 pancreatic cancer, highlighting the complexity of the interaction between exercise and tumor growth. Under both conditions, exercise did not have an additive effect; however, the combination of chemotherapy and exercise significantly improved treatment efficacy which suggests a sensitizing effect. Additional experiments showed that the delivery of a single dose of doxorubicin (after the last exercise session) to the interior of the B16F10 tumors was significantly increased in the mice that exercised compared to controls. Moreover, administration of doxorubicin immediately before a single bout of exercise did not improve the levels of the doxorubicin in the B16F10 tumors compared to controls. Taken together, these results suggest that the chronic effects of exercise on tumor vascularization and normalization may have a more significant impact on tumor blood perfusion than a single acute bout of exercise.

Emerging evidence from preclinical studies suggests many other biologically plausible systemic adaptations including changes in immune function, inflammation,

metabolism, and sex hormones, which may mediate changes in the tumor microenvironment and subsequently influence chemotherapy treatment efficacy or have direct effects on treatment response [50–52].

Very few clinical studies have examined the impact of exercise on chemotherapy response. In a subgroup analysis of patients receiving chemotherapy in the HELP trial [53] (a randomized controlled trial comparing usual care to 12 weeks of supervised exercise in lymphoma cancer survivors), the complete response rate was 46.4% (13/28) in the exercise group compared to 30.8% (8/26) in the usual care group. Although these findings were nonsignificant, they are noteworthy despite the small sample size. Lymphoma patients receiving chemotherapy all have multiple existing tumors; therefore, the possible mechanisms of improved vascularization and perfusion of the tumors apply in this clinical setting. In the neoadjuvant breast cancer setting, Jones et al. have demonstrated that aerobic exercise in conjunction with chemotherapy modulates systemic factors including endothelial progenitor cells, plasma cytokines, and plasma angiogenic factors which may enhance the effectiveness of anticancer drugs [54].

Moreover, exploratory long-term follow-up data from large exercise clinical trials suggests that exercise in the adjuvant chemotherapy setting may improve treatment response including disease-free survival (DFS) and overall survival (OS) in breast cancer survivors [55, 56] and progression-free survival in lymphoma cancer survivors [57]. In the previously mentioned START trial [55], the aerobic exercise training group and the resistance exercise training group were combined and compared to the usual care group on longer-term cancer outcomes. After a median follow-up of 89 months, there were 25/160 (15.6%) DFS events in the exercise groups compared to 18/82 (22%) in the control group. Eight-year DFS was 82.7% in the exercise groups compared to 75.6% in the control group. There were 20 (12.5%) recurrence-free interval (RFI) events in the exercise groups and 17 (20.7%) in the control group. The eight-year RFI incidence rate was 12.6% in the exercise groups and 21.6% in the control group. Although none of these observed effects were statistically significant, the magnitude of the effects could be meaningful. Moreover, exercise appeared to have a stronger effect on DFS (borderline significant effect) and RFI (significant effect) in women who received ≥85% of their planned chemotherapy (vs. <85%) which suggests that improved chemotherapy completion rate may not be the sole explanation for the improved outcomes. Finally, eight-year overall survival was 91.2% in the exercise groups compared to 82.7% in the control group (HR, 0.60; 95% CI, 0.27–1.33).

In Australia, data from the Exercise for Health trials were combined to examine their effects on survival outcomes [56]. Briefly, both trials were randomized and compared the effects of an 8-month pragmatic exercise intervention on function, side effects, and quality of life, compared to usual care; however, one trial was conducted in an urban setting and delivered either face-to-face or by telephone (randomized comparison), whereas the other trial was conducted in a rural setting and delivered by telephone [58, 59]. After a median follow-up of 8.3 years, there were more DFS events in the usual care group (23/130, 17.7%) compared to the exercise group (25/207, 12.1%) (adjusted HR, 0.65; 95% CI, 0.36–1.17; $p = 0.15$). Although not statistically

significant, there were 10 (7.7%) breast cancer-specific deaths in the usual care group compared to 10 (4.8%) in the exercise group. Furthermore, there were significantly more OS events in the usual care group (15/130, 11.5%) compared to the exercise group (11/207, 5.3%). Of note, the sample included women receiving a mix of adjuvant cancer treatments including chemotherapy, radiation therapy, hormone therapy, and Herceptin®. Although the groups were somewhat balanced at baseline for treatment types, it is unclear if all participants were receiving adjuvant treatment.

In longer-term follow-up of the HELP trial [57], patients who received supervised exercise (including those in the control group who crossed over), had an adjusted 5-year progression-free survival of 68.5% compared to 59.0% for the group that received no supervised exercise (HR = 0.70, 95% CI = 0.35–1.39, $p = 0.31$). Furthermore, exercise adherence in both the START and HELP trials was not optimal, suggesting the potential for even larger effects with improved adherence. Nevertheless, the data from these studies provide support for trials with adequate sample size to detect differences in treatment efficacy outcomes.

The nature of the effects of exercise on treatment efficacy is difficult to disentangle in human clinical trials because (a) it is often unknown whether exercise has direct effects on tumor growth and metastases in humans and (b) it is often impossible to randomize cancer patients to exercise alone. Consequently, if exercise during cancer treatment improved cancer outcomes, it would be unclear if it were a sensitizing, synergistic, or additive effect. Animal studies can answer these questions more clearly, but their generalizability to clinical contexts is obviously limited.

Radiation Therapy

Tumor hypoxia has been identified as a key factor limiting the effectiveness of radiation therapy as radiation cannot induce tumor cell DNA damage without sufficient oxygen [60, 61]. The characteristics of the TME that cause chemotherapy drug resistance also cause tumor hypoxia, and preclinical studies have demonstrated that repeated bouts of exercise improve the delivery of oxygen to the interior of the tumor through the same mechanisms as chemotherapy drug delivery (i.e., angiogenesis and improved blood perfusion) [44, 62]. Moreover, McCullough et al. demonstrated that a single bout of exercise improved intratumoral blood perfusion by 200% and subsequently reduced tumor hypoxia by 50% in a preclinical orthotopic prostate cancer model [45]. This response is somewhat unexpected, given what we know about the redirection of blood flow to active skeletal muscle during exercise. Wiggins et al. have suggested that this response may be explained by tumor vessels' inability to respond to vasoconstrictive signals and therefore benefiting from the increase in cardiac output and oxygen supply that occur during exercise [63]. To date, very little is known about how exercise may mediate the response to radiation therapy in patients, and no exercise intervention trials have included radiation response as an outcome.

Hormone Therapy

It is unclear if exercise can improve the efficacy of hormone therapy. It is possible, however, that exercise may have an added benefit in women with hormone-sensitive breast cancer. Higher levels of physical activity after a breast cancer diagnosis have been associated with a lower risk of recurrence [64]. In postmenopausal women, moderate-intensity exercise, compared to control, decreases circulating levels of sex hormones including estrogens and androgens with even larger effects observed when fat loss is achieved [65]. Therefore, it is possible that exercise may reduce recurrence in women with breast cancer by improving circulating hormone levels and/or inducing fat loss. The effects of exercise on hormone treatment efficacy in men with prostate cancer are unknown.

Immunotherapy

As noted earlier, several types of immunotherapy exist and are associated with positive outcomes for patients. Through complex mechanisms, immunotherapies help the immune system detect and destroy cancer cells, thereby stopping or slowing the growth of cancer and preventing the development of metastatic disease. Moreover, conjugated monoclonal antibodies can be used to help deliver radiation or chemotherapy to the cancer cells. Exercise training induces systemic changes in circulating immune cells; however, the impact of these changes on the TME and immunotherapy is unclear. Some groups have proposed that exercise-mediated changes in the TME may improve response rates to immunotherapy through various pathways. For instance, as Aschcraft et al. [50] and Christensen et al. [18] have pointed out, exercise-mediated improvements in tumor hypoxia and tumor metabolism may improve immune cell infiltration and ultimately the delivery and effectiveness of checkpoint inhibitors. Contrarily, Hojman et al. [51] have pointed out the potential negative effects of exercise on response to certain types of immunotherapy (e.g., anti-angiogenic therapies) where the goal of treatment is to reduce blood flow to the tumor. To date, no exercise studies have examined the impact of exercise on response to immunotherapy in cancer patients; however, given the strong rationale for benefit or harm, preclinical and clinical studies are warranted.

Summary and Future Directions

Treatment Completion

Chemotherapy, radiation therapy, hormone therapy, and immunotherapy cause toxicities which may interfere with patients' ability and willingness to successfully complete their treatments. Exercise appears to mitigate some of the side effects

of cancer treatments and may improve treatment completion rates. Treatment-related side effects which result in dose modifications will vary according to cancer type, treatment timing (neoadjuvant vs. adjuvant), treatment regimen (e.g., radiation alone vs. radiation in combination with chemotherapy, chemotherapy alone vs. chemotherapy in combination with immunotherapy), and individual factors. Therefore, it is imperative that research examine the effects of exercise on treatment completion rates in various clinical cancer settings. To date, there is some evidence that exercise may improve chemotherapy completion rates; however, the data are restricted to early stage breast cancer patients. Moreover, sarcopenia and sarcopenic obesity are emerging as a determinants of dose-limiting treatment toxicities across various cancer types and chemotherapy drugs and may be important targets for future exercise intervention trials. Nevertheless, much more research on the determinants of chemotherapy treatment completion in various cancer settings is needed in order to develop targeted exercise interventions. Moreover, this research needs to be expanded to other cancer treatment modalities including radiation therapy, hormone therapy, and possibly immunotherapy where dose-limiting toxicities and the safety of exercise may differ. For example, exercise has the potential to make dermatologic toxicities from radiation therapy worse depending on the site that is being irradiated and the type of exercise prescribed. Additionally, exercise intervention studies designed to compare the effects of different types of exercise (i.e., aerobic vs. resistance vs. combined vs. usual care) on cancer treatment completion are warranted. Finally, more research is needed to determine the optimal timing of exercise relative to cancer treatment. For example, is exercising during chemotherapy infusion or immediately prior to radiation therapy safe and feasible, and does it improve dose-limiting treatment toxicities?

Treatment Efficacy

Although multiple preclinical studies have shown that exercise training regulates several of the pathways involved in chemotherapy resistance, research demonstrating that these improvements translate into therapeutic benefit is limited, and even less is known about the potential impact of exercise on treatment efficacy for other cancer treatment modalities including radiation therapy and immunotherapy. The effects of exercise on cancer treatment response may be impacted by the location of the tumor, the timing of the intervention relative to treatment (i.e., before, during, or after), the treatment regimen, and individual factors (i.e., biomarkers).

Consideration should be given to how we measure treatment efficacy in exercise intervention trials. For one, the outcomes will differ based on the timing of the intervention. In the neoadjuvant and metastatic settings where the goal of treatment is to shrink the tumor(s), response to the treatment might be evaluated using tumor volume or clinical downsizing. In the adjuvant setting where the goal is to eradicate residual tumor cells, survival-related outcomes with longer-term follow-up will be required. The use of traditional efficacy endpoints (e.g., DFS, PFS, OS) to assess cancer treatment response rates in exercise intervention trials poses similar

limitation to clinical trials. For example, a large sample size is required, and the longer-term follow-up is often confounded by exercise crossover.

Moreover, measuring the effects of exercise on treatment response may be challenging as exercise has the potential to mediate traditional efficacy endpoints independently of its interaction effect with cancer treatments (see Figs. 10.1 and 10.2). Exercise, as an adjuvant therapy, may control cancer progression/recurrence through its direct effects on tumor growth and metastases or by interacting with existing cancer treatments. Distinguishing between an additive effect and interaction effect of exercise on these traditional efficacy endpoints is difficult as it would require a factorial design with four groups (i.e., drug only, exercise only, both, and neither). Research in preclinical models supports the possibility of additive, sensitizing, and synergistic effects of exercise on disease outcomes. Designing similar trials in humans will require "window of opportunity" studies where a new treatment is compared to placebo/no treatment with additional randomization to exercise versus no exercise.

It may be feasible to examine the effects of exercise on treatment response in the neoadjuvant setting; however, it will still be unclear if the effect is additive, sensitizing, synergistic, or even antagonistic. Moreover, it may be feasible to study the direct effects of exercise on disease progression in the active surveillance setting (e.g., prostate and colon cancer). As illustrated by the animal studies reviewed in this chapter, the potential interactions between exercise and treatment response are complex, and we cannot assume that exercise will be beneficial. At a minimum, exercise intervention trials during cancer treatment should be tracking treatment response to ensure that exercise is not negatively impacting cancer treatment response rates.

Another important consideration for exercise trials is the timing of the exercise relative to cancer treatment. If an acute bout of exercise does substantially increase tumor blood perfusion and reduce tumor hypoxia, then exercising immediately before or after, or even during cancer treatment, may be optimal. While exercising during a chemotherapy infusion seems feasible, it is unclear if exercising during, or even immediately before, radiation therapy is feasible. It is also possible that the acute effects of exercise may not significantly improve blood perfusion and that changes may be driven by the chronic effects of exercise training. If that is the case, then the timing of the exercise relative to treatment delivery may not be as critical.

Finally, given the challenges of designing resistance training exercise interventions in rodents, the effects of this exercise modality on the TME are unknown. Nevertheless, resistance training has the potential to induce favorable changes that could lead to improvements in the effectiveness of cancer treatments. For example, resistance training has the potential to optimize changes in body composition which could lead to better drug distribution and hence effectiveness. Much more work is needed before we can start to examine the optimal exercise prescription (i.e., frequency, intensity, duration, and type) for improving cancer treatment response rates.

Conclusion

Exercise is an effective strategy for improving physical fitness, symptoms, and quality of life in several cancer patient groups. Nonetheless, it is unclear if exercise can improve treatment and disease outcomes. This chapter highlights preliminary research demonstrating the potential for exercise-mediated improvements in treatment completion and treatment efficacy. Moreover, multiple preclinical studies have shown that exercise has direct effects on tumor growth and disease progression. Although this research is promising, no study to date has been designed to answer the questions related to treatment completion and efficacy in actual patients.

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Part III
Post-treatment to End of Life

Chapter 11
Exercise Oncology from Post-treatment to End of Life: An Overview of Outcomes and Considerations

Kira Bloomquist and Sandra C. Hayes

Introduction

Cancer incidence is growing worldwide, and it is estimated that 18.1 million people were diagnosed with cancer in 2018, affecting one in five men and one in six women [1, 2]. Globally, while 9.6 million deaths were attributed to cancer annually, 5-year prevalence data estimate that 43.8 million people are living beyond a cancer diagnosis, with the five most frequent cancers diagnosed being lung, breast, prostate, stomach, and liver cancers (excluding nonmelanoma skin cancer) [1]. Survival rates following cancer vary worldwide within and between cancer types. For example, 5-year survival rates range from 5–15% for pancreatic cancer to 66–90% for breast cancer depending on the country [3]. In general though, survival rates globally have improved, especially in countries where cancer can be detected early and access to improved treatment strategies is readily available [3, 4].

The time at which treatment for cancer ends represents the beginning of the post-treatment cancer survivorship phase [5]. While this phase is characterized by the absence of "cancer treatment", long-term pharmacological interventions, such as hormone therapy for hormone-responsive cancer types and bisphosphonates and denosumab to reverse or stabilize bone loss associated with a specific cancer or treatment received, may continue during this phase. For some, the post-treatment phase represents treatment success, whereby a patient no longer has any evidence of cancer and risk of recurrence is low (defining the time point when a patient may consider themselves as 'someone who once had cancer' or as a 'cancer survivor') [6].

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For others, the post-treatment phase may represent a temporary period before initiation of a new round of treatment, with curative or prevention of progression intent. For others still, the post-treatment phase starts when the benefits of continuing cancer treatment no longer outweigh the adverse effects it causes. In these instances, it may mark the time at which a patient commences palliative care and the purpose of treatment received seeks to improve quality of life through alleviation of disease-related side effects and symptoms. Throughout this chapter, we refer to all patients who have completed cancer treatment as a 'cancer survivor' while acknowledging that not all relate with this term [7].

Cancer and cancer treatment are associated with adverse changes to physiological systems (e.g., cardiovascular, musculoskeletal, endocrine, lymphatic), which precede the onset of treatment-related side effects and observed declines in function, quality of life, and survival (Fig. 11.1). Notably, the adverse physiological effects associated with cancer or its treatment are similar to that which occur with aging. As such, the cumulative effects of cancer, its treatment, and aging contribute to an accelerated aging effect [8–10]. Indeed, physiological changes that are ordinarily observed over a 10-year or more period of aging have been measured with in the first year following a cancer diagnosis. As such, with more people surviving cancer or living longer with a cancer diagnosis, these survivorship issues reflect a growing global health concern.

A consistent and compelling body of evidence demonstrates that influencing physical activity levels post-treatment, in particular through exercise, can counteract the adverse physiological changes that occur during the treatment period [11–14]. Specifically, higher physical activity levels post-cancer and exercise intervention post-treatment have been associated with lower number and severity of persistent treatment-related side effects, prevention and better management of late treatment-related side effects, and improved function, quality of life and survival (Fig. 11.1). Outlined below is a summary of survivorship concerns experienced during the post-treatment phase and the potential role of physical activity in this phase.

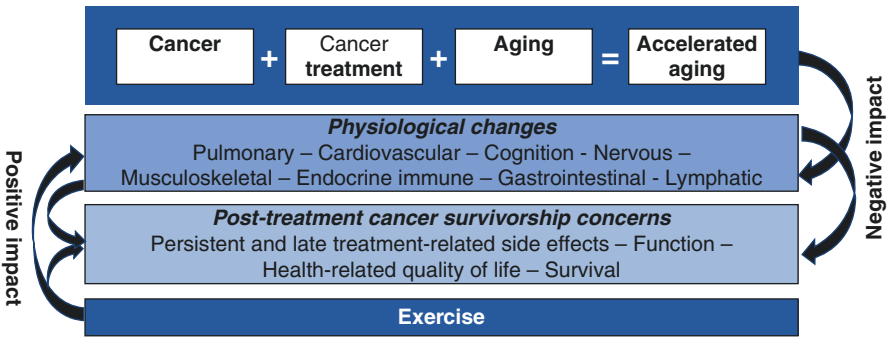

Fig. 11.1 The inter-relationship between cancer, treatment and aging, and the role of exercise in counteracting physiological changes associated with accelerated aging and post-treatment cancer survivorship concerns

Post-treatment Cancer Survivorship Outcomes

We describe here post-treatment cancer survivorship concerns within the framework outlined in Fig. 11.1: persistent and late treatment-related side effects, function, quality of life, and survival.

Persistent and Late Treatment-Related Side Effects

While a subgroup of cancer survivors return to 'normal' after the completion of treatment and are able to live relatively symptom-free lives, others have persistent treatment-related side effects that do not recede with time (Fig. 11.2). These concerns emerge during treatment and persist in a chronic, long-term manner and may include one or more physical and psychological conditions, such as neuropathies (with related weakness), pain, fatigue, lymphedema, cognitive difficulties, sexual dysfunction, and elevated levels of anxiety or depression [15, 16]. Late treatment-related side effects is a term used to describe symptoms and conditions that develop as a consequence of adverse treatment effects on organ systems or psychological processes but appear months or years following treatment rather than during the treatment period (Fig. 11.2) [15, 16]. These could include concerns related to bone health (e.g., osteopenia, osteoporosis), lymphedema, cardiovascular-related issues, or psychosocial issues (e.g., fear of cancer recurrence). Fatigue, pain, and psychosocial issues (e.g., anxiety, distress, depression) are considered some of the more common post-treatment side effects [16] and are explored in more detail below:

Cancer-related fatigue: Cancer-related fatigue has been defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or

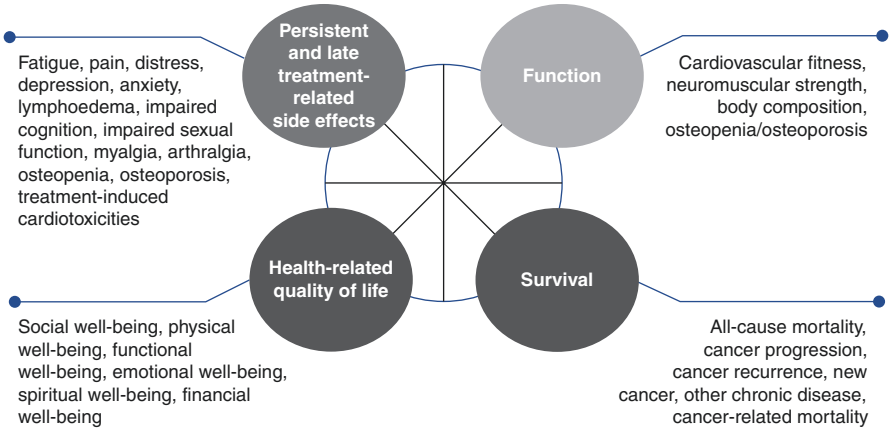

Fig. 11.2 Inter-relationships between treatment-related side effects, function, health-related quality of life and survival in the post-treatment cancer survivorship phase

exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [17].While cancer-related fatigue is reported more frequently than any other symptom during the course of cancer and its treatment [17–19], cancer survivors may experience fatigue for months to years after treatment cessation. For example, in an observational study from 2016, approximately one-third of a sample of breast, colorectal, and prostate cancer survivors (n = 1294) reported clinically relevant levels of fatigue (associated with high levels of disability) up to 6 years post-treatment [20]. Similarly, in a cross-sectional study including breast, prostate, colorectal, and lung cancer survivors (n = 515), with no evidence of disease and not currently receiving cancer treatment (median time since diagnosis 27 months, range 0–454), moderate to severe fatigue was reported by approximately one-third of the sample [19]. In cancer survivors with metastatic disease, the prevalence of fatigue has been found to exceed 75% [17]. Cancer-related fatigue is often cited as the most distressing symptom related to cancer or cancer treatment, primarily because of its persistence and interference with multiple aspects of daily life [17]. Importantly, it should be noted that fatigue most commonly does not present alone but rather presents alongside other symptoms, such as pain, emotional distress, and sleep disturbance (known as a symptom cluster) [17, 21].

Pain: Cancer-related pain is often multifactorial, with the malignancy, oncologic treatments, and psychosocial and spiritual distress contributing to the presence and severity of nociceptive and neuropathic pain [22]. It is considered one of the most feared cancer-related adverse effects (with its management a major focus of palliative care), and while it is not an inevitable consequence for all cancer types and treatments, it is common [22]. Indeed, a meta-analysis from 2016 including 117 studies (n = 63,533) reported a prevalence of pain in 40% of the sample post-treatment. In studies reporting on severity of pain (52 studies, n = 32,261), almost one-third of cancer survivors rated pain levels as moderate to severe after cessation of treatment [23]. In cancer survivors with advanced cancer, two-thirds reported pain, and over half of these rated its severity as moderate to severe [23]. This high prevalence of pain is particularly noteworthy since unrelieved cancer-related pain affects all aspects of daily living with negative ramifications for quality of life. Further, evidence supports that effective pain management improves quality of life and ultimately survival [24].

Distress, anxiety, and depression: Compared with age-matched, healthy controls, cancer survivors have an increased risk of developing anxiety, depression, and other mental health issues including distress [16, 25]. The National Comprehensive Cancer Network defines distress as “a multifactorial unpleasant experience of a psychological (e.g. cognitive, behavioral, emotional), social, spiritual or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment” [16, 26]. Distress is often

related to fear of cancer recurrence, and while it is not a psychiatric clinical diagnosis, it can exert a significant negative impact on quality of life and can lead to severe psychological morbidity. Indeed, fear of recurrence (experienced by up to 80% of cancer survivors), alongside persistent emotional distress, has been identified as major contributors to the presence of clinical anxiety and/or depression.

The timing of initial presentation of an adverse effect and the distinction between persistent and late effects can be blurry. Nonetheless, it is estimated that at least 50% of cancer survivors experience treatment-related sequelae throughout the post-treatment survivorship phase [16]. For example, an Australian population-based, longitudinal breast cancer cohort study (n = 287) that assessed the presence of nine treatment-related survivorship concerns found that while the prevalence of any given side effect (of at least moderate severity) at the 6-year follow-up ranged between 6% and 24%, over 60% of women reported *at least one* treatment-related side effect at that time [21]. Further, the presence of one symptom increased the likelihood of reporting additional symptoms (i.e., reporting two or more symptoms was more common than one symptom alone). When side effects reported as mild in severity were also included in the analysis, the proportion experiencing late or persistent treatment-related side effects rose further. For those with advanced stage cancer, the prevalence and severity of treatment-related side effects are even higher, making symptom burden the greatest contributor to lower quality of life [27]. For example, in a sample of 977 preterminal cancer survivors with advanced disease, approximately 50% reported problems with everyday activities, and 92% reported at least one physical impairment [28].

The type and severity of any given post-treatment side effect are likely influenced by patient characteristics (including age, body mass index, socioeconomic status, race, income) and behavioral characteristics (such as physical activity levels, smoking, nutritional status), as well as specific characteristics related to the cancer diagnosis (type, stage, hormone status). Further, the type of treatment received (e.g., surgery, radiation, chemotherapy, hormonal, other) and its characteristics (e.g., duration, dose, invasiveness) are also directly related to the type and severity of potential side effects [15, 19, 22, 26, 29]. Consequently, as treatments for cancer have evolved, so too have the type and severity of adverse effects that present. Notably, despite treatment advances contributing to survival gains, the prevalence of persistent and late effects in cancer survivors remains common and is potentially increasing [16]. This situation may be a consequence of the delivery of more complex and intense treatments, with new combinations of surgery, radiation therapy, chemotherapy, endocrine therapy, immunotherapy, and targeted biological treatments representing advances in treatment [16]. It is also plausible that as survival rates improve, so too does our ability to detect and monitor the presence and impact of persistent or late treatment-related survivorship concerns (see Chaps. 12 and 13 for more details).

Function

Physical function is the ability of individuals to perform basic actions that are essential for maintaining independent living and carrying out more complex activities [30]. Functional status can be measured via self-reported methods or through functional testing of, for example, cardiovascular/respiratory fitness, neuromuscular strength and endurance, body composition, range of motion, and balance (Fig. 11.2). Summarized below are treatment-associated changes in bone health, cardiovascular function, and body composition that are relevant in the post-treatment cancer survivorship phase.

Bone health: Bone health issues, specifically osteopenia, osteoporosis, and subsequent increased risk for fractures, have functional ramifications, in particular for cancer cohorts/subtypes receiving specific chemotherapy and endocrine therapies that decrease circulating sex steroids [31]. For example, it has been estimated that annual rates of bone loss at the spine from chemotherapy, aromatase inhibitors (breast cancer), and androgen deprivation therapy (prostate cancer) average 7%, 3%, and 4%, respectively [31]. This rate of bone loss is of clinical relevance since small declines of 3–5% in bone mass may increase future risk of fracture [32]. Indeed, compared with non-cancer populations, lower levels of bone mass density and higher incidence of fractures have been found in several cancer populations (independent of metastatic disease), with subsequent adverse effects on morbidity and survival [32, 33].

Cardiovascular function: Survivors of some cancer types have a significantly increased risk of developing cardiovascular disease as a result of toxicities related to certain cancer treatments [34]. For example, up to 50% of cancer survivors who have received anthracyclines may experience asymptomatic left ventricular fraction decline. Further, anthracycline-induced heart failure may manifest years post-treatment, while other systemic therapies, such as HER2-targeted treatments, immunotherapies, and angiogenesis inhibitors, also are associated with increased risk of cardiomyopathies [16]. Of note, low cardiorespiratory fitness has been implicated in the etiology of certain treatment-induced cardiovascular late effects and is a predictor of anthracycline- and trastuzumab-induced left ventricular dysfunction [34]. This impact on cardiovascular function is relevant since reductions in cardiorespiratory fitness have been observed post-treatment, with fitness estimates 30% below that of age- and sex-matched sedentary individuals without a history of cancer [35]. As such, efforts to prevent declines and/or improve fitness following a cancer diagnosis, particularly for those with low levels of fitness at diagnosis, are warranted. The emerging area of "cardio-oncology" is discussed in greater detail in Chap. 14.

Adverse body composition changes: Sarcopenia, which is defined as progressive and generalized loss of skeletal muscle mass and strength, has been

identified as a cancer survivorship concern across multiple cancer types, irrespective of disease stage and nutritional status [36]. It is associated with sarcopenic obesity, which is characterized by increased fat mass in the presence of no change or decreases in muscle mass, or cancer cachexia, which is characterized by loss of muscle mass accompanied by unintentional loss of body weight. Overall, the prevalence of sarcopenic obesity has been estimated at 9% (range, 2–15%) in advanced solid tumor patient populations but has been most heavily documented in women with breast cancer [37]. Cancer cachexia, on the other hand, tends to be more prevalent in those with lung, colon, and pancreatic cancers and cancers (or subgroups within specific cancers) associated with poor prognosis, more advanced stage at diagnosis, and the presence of one or more disorders including systemic inflammation, insulin resistance, anemia, hypogonadism, and anorexia [38]. Irrespective of whether or not sarcopenia presents with or without weight change (gain or loss), adverse changes in body composition have been associated with higher morbidity (including strength and functional losses) and mortality [36, 37] and will be discussed in greater detail later in this book (Chap. 15).

Understanding function post-treatment is particularly relevant since (a) lower function is associated with lower quality of life [39], (b) physical function and fitness are considered prognostic factors of survival [40], and (c) an opportunity exists to describe and quantify the effects of cancer and cancer treatment on physical abilities considered essential for maintaining independence (such as walking or reaching), which in turn can guide the role of physical activity, including exercise, in rehabilitation [41].

Health-Related Quality of Life

While there is no commonly accepted definition of what constitutes health-related quality of life, there is broad consensus that it is a patient-reported, multidimensional construct encompassing domains including physical, functional, emotional, financial, social, and spiritual domains (Fig. 11.2) [42]. Changes in social interactions (either due to a cancer survivor withdrawing from their social environments or a cancer survivor's social network withdrawing from them), financial issues (potentially due to medical costs or to loss of income related to sick leave), loss of function (with notable effects to physical/functional domains), and the presence of treatment-related side effects (including persistent and late effects) represent just some examples that may contribute to declines in quality of life in the post-treatment phase [42, 43]. Importantly, while assessments of health-related quality of life and its domains provide an overall measure of the quality of cancer survivorship, health-related quality of life also has prognostic and predictive significance, with lower quality of life being associated with reduced survival [42].

Survival

Low physical activity levels, smoking, and being overweight or obese represent modifiable risk factors for the development of cancer (in particular for common cancers, such as breast, colorectal, and prostate) [44], as well as other common chronic diseases, such as osteoporosis[45], type II diabetes, cardiovascular disease, and stroke [46]. Post-cancer, risk of developing new cancers or other chronic disease may be increased further through direct and interrelated adverse effects of cancer treatment on physiological systems (as described above, Fig. 11.1), through the impact of persistent and late treatment-related side effects on function and quality of life (Figs. 11.1 and 11.2), and/or due to adverse changes in modifiable behaviors (such as physical activity). Moreover, the presence of pre-existing comorbidities at diagnosis of cancer (e.g., overweight or obese) may influence the type and dosage of treatment received, with receipt of suboptimal treatment linked with reduced survival outcomes (e.g., risk of developing cancer recurrence, progression of disease or new cancer or chronic disease, and risk of dying from all-cause mortality or cancer-specific cause) [47]. As such, strategies that show potential for improving *quality of survival*, through prevention of treatment-related sequelae, improvements in function and quality of life, and improvement in pre-existing comorbidities or other chronic disease, have the potential for improving *quantity of survival*, both directly and indirectly.

Considerations for Exercise in the Post-treatment Setting

As noted above, low physical activity levels are a known risk factor for many cancers [44]. Evidence demonstrating that more than half of those diagnosed with cancer are physically inactive (i.e., engage in less than 150 minutes of moderate-intensity physical activity per week) is therefore not surprising [48]. Notably, the majority of cancer survivors will also experience declines in physical activity following diagnosis [48, 49]. Consequently, there is capacity and opportunity for improving cancer survivorship through physical activity promotion and exercise intervention.

To understand the potential role of exercise in the post-treatment phase, it is first necessary to consider typical survivorship trajectories observed following treatment. Figure 11.3 highlights that at the time of treatment cessation, on average, cancer survivors have lower function compared with age-matched healthy controls [16, 41]. For some, the cessation of treatment may allow a gradual return to daily activities and regain in function (labeled in Fig. 11.3 as ‘Increase’). However, without targeted or planned physical intervention, it is unlikely for function to return to levels that are commensurate with age-matched controls. For others, losses experienced during treatment may reflect their new ‘state of normal’ post-treatment (labeled as ‘Maintain’ in Fig. 11.3). For others still, in particular those with advanced disease, losses in function continue throughout the

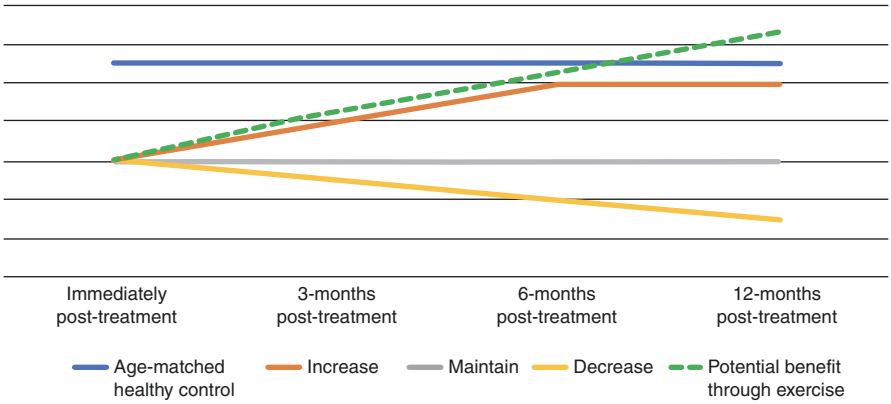

Fig. 11.3 Post-treatment cancer survivorship trajectories for function and potential for exercise to modify these trajectories

post-treatment phase (labeled as 'Decrease' in Fig. 11.3). While these groupings simplify cancer survivorship trajectories experienced, the intent is simply to provide a crude example of what may broadly be experienced with respect to function throughout the post-treatment phase. In turn, this schematic helps set the scene for describing the potential for physical activity levels and exercise intervention to modify these trajectories.

A compelling and consistent body of cohort and trial evidence describes the significant benefits to be gained by incorporating exercise as part of cancer management post-treatment. Indeed, more than 140 systematic reviews summarizing findings of exercise and oncology trials have found that exercise facilitates physical and mental recovery and may prevent and/or improve management of persistent and late treatment-related side effects and existing comorbid conditions [11–13]. Further, exercise post-treatment leads to improvements in function (self-reported, fitness and strength) and quality of life, with magnitude of effect being sufficient that it is possible for function and quality of life to exceed that observed at pre-diagnosis and of age-matched healthy controls (as shown by the dotted line in Fig. 11.3). In addition, there is compelling evidence from high-quality cohort studies that higher levels of physical activity post-treatment are associated with improved survival [50]. This evidence is now supported by preliminary findings from Phase 2 exploratory trials that show positive effects through exercise intervention on survival outcomes in breast cancer [51, 52], leukemia [53], and lymphoma [54]. As such, the potential for exercise to prevent further declines, extend the duration of maintaining, or stimulate gains in function and quality of life after treatment is great, with positive effects extending to treatment-related side effects and potentially survival. However, a number of factors must be considered to ensure benefit through exercise without increasing cancer survivorship burden.

Feasibility and safety considerations for exercise: The number of persistent and late treatment-related side effects that have been evaluated as outcomes in oncology

exercise trials is extensive, although some outcomes (such as fatigue and lymphedema) have received more attention than others (e.g., myalgia, chemotherapy-induced peripheral neuropathy) [11]. The attention given to fatigue and lymphedema is at least in part due to concerns that exercise may precipitate or worsen these treatment-related side effects. However, there now exists moderate to strong evidence demonstrating that (1) exercise does not increase the risk of developing breast cancer-related lymphedema; (2) exercise improves lymphedema-associated symptoms (such as weakness, pain, tiredness) and may improve lymphedema management [55, 56]; and (3) exercise is considered one of the most effective non-pharmacological treatments for fatigue [57]. Conversely, low levels of physical activity have been associated with increased risk of developing or worsening lymphedema and fatigue [17, 29]. While research examining the relationship between exercise and persistent and late treatment-related side effects continues, to date, the evidence supports exercise as being an important strategy for improving function and quality of life while either likely improving treatment-related side effects or, at the very least, not making them worse.

Risk of serious adverse events in exercise oncology trials has been reported as low (<5%), and there have been no life-threatening adverse events or deaths [11, 12, 58]. Further, of the studies that report on exercise-related adverse events, the vast majority (80%) have indicated none occurred. In addition, withdrawal rates from exercise intervention trials are generally low (<10%), and adherence to the exercise intervention is generally high (>80%) [58, 59]. These safety and feasibility findings remain consistent even when reviews have focused on cancer cohorts with more advanced disease and higher risk of harm (e.g., due to the presence or risk of treatment-related side effects) [59]. However, these findings need to be considered in light of the limitations of the contributing evidence base. Specifically, samples involved in exercise oncology trials tend to be younger, be more physically active, and have early stage disease, compared with the wider cancer population (i.e., there are limitations to the representativeness of cancer samples studied to date). Further, the presence of specific treatment-related side effects (e.g., unstable lymphedema) or other chronic disease or comorbidity (e.g., hypertension) may represent exclusion criteria for specific trials, which again reduces the potential representativeness of safety and feasibility findings to the wider cancer community. In addition, while the number of cancer types evaluated in exercise trials has increased over the past decade, there remain a preponderance of trials involving women with breast cancer [11, 12]and a paucity of trials involving cancer samples with more advanced disease [60, 61]. Further, feasibility findings come from heterogeneous assessments of adherence and compliance to prescribed and completed exercise, and while mean feasibility for any given sample may be high, the range for individuals within a given sample is wide (e.g., 0–100%) [62]. Indeed, it is clear that adherence and compliance to an exercise prescription are influenced by personal and treatment-related factors (such as presence and severity of persistent and late effects), as well as other medical-related and behavioral factors [63]. These represent important considerations when seeking to improve cancer survivorship through exercise.

Physical activity promotion and exercise prescription: To promote the effects of physical activity, various cancer organizations recommend that cancer survivors meet physical activity guidelines promoted to the general adult population; ≥150 minutes of at least moderate-intensity physical activity/week, plus muscle strengthening activities at least two times per week [64, 65]. However, factors noted above, including functional status and likely survivorship trajectory (in function, quality of life, and survival), presence of persistent and late treatment-related side effects, and individual (disease, treatment, behavioral, etc.) factors, will influence whether these physical activity targets are appropriate or achievable (in the short or longer term) for any given survivor.

As shown in Fig. 11.4, striving to achieve (and maintain) physical activity levels consistent with physical activity guidelines is likely appropriate for a cancer survivor with no persistent treatment-related side effects (or low impact of side effects on daily activities) and low risk of developing late effects and who is generally otherwise healthy (i.e., has no or low risk of developing new disease or comorbidities), has good and improving function and quality of life, and has good prognosis. However, as noted above, the majority of cancer survivors have at least one persistent or late treatment-related side effect, are insufficiently active, may present with additional comorbidities or chronic disease (or are at a higher risk of new disease), and commence the post-treatment survivorship phase with low function and quality of life (compared with age-matched controls). As such, for these cancer survivors, referral to an allied health professional, with specialist skills and knowledge in oncology exercise prescription, would be ideal.

Since publication of the first exercise and cancer position stands in 2009 [66] and 2010[64], there has been exponential growth in the number and quality of exercise

Post-treatment cancer survivorship phase		
High number or severtiy	Presence (or risk of new) and severity of persistent or late treatment-related side effects	None/no interruption to daily activities
Complex	Presence (or risk of new) chronic disease or comorbidities	Generally otherwise healthy
Low	Function	High
Low	Quality of life	High
Poor	Survival prospects	Good
Likely limited	Applicability of physical activity guidelines	Likely high
Likely high	Need for referral for exercise prescription and support	May be unnecessary

Fig. 11.4 Factors in the post-treatment cancer survivorship phase that influence the applicability of generic physical activity guidelines and potential need for referral for exercise prescription

oncology studies. The design of the exercise intervention evaluated in these trials (i.e., setting, degree of supervision, mode, and total exercise dosage evaluated) can be used to provide guidance to the recommended exercise prescription for a cancer survivor post-treatment. Exercise interventions have been conducted in a variety of settings (e.g., hospital-, clinic-, home-, or community-based) with no evidence to suggest the superior impact of one setting over the other [11]. However, there is evidence to suggest superior benefits (at least in the short term) in a variety of outcomes including adherence to exercise, quality of life, and function, when the program is supervised [11, 13]. Nonetheless, considerations to access and affordability of exercise prescription services will influence the extent to which supervision can be provided.

For the majority, the recommended exercise prescription will include aerobic and resistance exercise [67]. However, exercise goals (in particular goals linked to treatment-related side effects, function, quality of life, and survival) will influence the priority of any specific mode. The starting exercise dosage will be dependent on function and may comprise multiple short bouts of daily exercise, through exercise sessions of longer duration (e.g., 60 minutes) at least 3 days per week. Recommended exercise intensity to achieve benefit in outcomes such as fitness, strength, and function is generally moderate to high. However, low-intensity exercise should not be discounted, as it may be considered more achievable for specific groups (e.g., those near end of life) and has been associated with benefits in deconditioned individuals over time and improvements in cancer-related fatigue and overall physical function [11]. Pace of progression and degree of overload within and across sessions should be symptom-guided (when relevant) and allow for flexibility to accommodate cancer-specific considerations (e.g., fluctuations in treatment-related side effects such as a lymphedema flare-up or phase of worsening fatigue).

Of primary importance is that the cancer survivor remains central to the exercise prescription and with support and advice can define their exercise prescription goals while developing the necessary skills to achieve these goals [66, 67]. This approach means that individual preferences with respect to exercise mode, frequency, duration, and intensity of sessions should be considered and that the allied health professional works with a cancer survivor to identify an individualized, exercise prescription that enables achievement of short- and long-term exercise-related goals. A beneficial exercise program is one that a cancer survivor is able and willing to do.

Although the role of exercise for those receiving palliative care has been less extensively investigated, interventions including resistance exercise, aerobic exercise, and multimodal training (aerobic and resistance) have been found to elicit significant improvements in outcomes including physical function, fatigue, quality of life, body composition, and sleep quality [60]. Prognosis for those with advanced cancers varies widely, with progress in cancer treatment contributing to improvements in life expectancy even when curative treatment is no longer an option. Therefore, the role of exercise in improving, maintaining, or reducing declines in function and quality of life for those with advanced cancer should not be

underestimated. Nonetheless, the goals of exercise prescription must be tailored to meet the changing needs as cancer progresses to end of life. Exercise oncology for those with advanced stage disease is explored in more detail in Chap. 16.

Making a Difference to Cancer Survivorship

Improving cancer survivorship through systematic inclusion of exercise into cancer care will likely require additional research (particularly research that demonstrates exercise effect on survival, treatment compliance, and cost-effectiveness outcomes) and clinical and consumer advocacy and health policy changes. Nonetheless, the expansion of the evidence base over the previous decade has enabled updates [67–69] to the original exercise and cancer prescription guidelines [64, 66]. These updates describe how cancer survivorship can be improved immediately through promotion of the importance and benefits of staying or becoming physically active post-treatment to all cancer survivors. That is, all members of the cancer team (clinician, nurses, allied health professionals) can and should encourage survivors to *move more* and *sit less*. For those who were insufficiently active prior to and/or during their cancer treatment, they should be reassured that it is *never too late* to benefit through increasing physical activity levels [69]. When appropriate, available, and accessible, referral to allied health professionals with exercise oncology expertise would allow for individualized, exercise prescription designed around cancer survivor-driven goals [67, 68]. Finally, the number of cancer-specific exercise programs available worldwide is growing and provides options for the ways in which the increasing cancer survivorship population can benefit through physical activity, including exercise [70].

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Chapter 12
Immediate Posttreatment Period

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The purpose of this chapter is to provide an overview of how exercise may be incorporated into the care and management of cancer survivors during the immediate posttreatment period. The immediate posttreatment period would describe the survivor's physical and emotional health status when primary adjuvant treatment is completed up to the first year of recovery. Exercise may help the survivor recover from treatment by alleviating or mitigating side effects and symptoms that have not yet resolved with treatment completion. Exercise can also address the deconditioning that commonly occurs across the treatment period and be used as a strategy to help the survivor return to normal living or even better since the posttreatment period is considered a window of opportunity for making positive behavior change [8]. Some side effects and symptoms may never completely resolve, so learning how to exercise in spite of persistent impairments or limitations is also a worthwhile objective and will be part of continued discussion in the next chapter. Some cancers are also treated with additional antihormone therapy, targeted therapy, or immunotherapy that begins at the end of primary adjuvant treatment, so exercise began at this time period may be able to minimize side effects and symptoms associated with long-term therapies but also needs to consider how these treatments affect exercise tolerance. Since new treatments are always on the horizon and the full side effect profile and impact on exercise tolerance may not be immediately known when these therapies are used in clinical practice, the fitness professional should always be seeking information about advances in cancer treatment. Perhaps the most important consideration for the fitness professional working with a survivor during the immediate posttreatment period is to understand the potential depth and breadth

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of the physical and emotional toll that cancer takes on an individual and how that affects their ability to exercise and their need for exercise. By inventorying every survivor client to learn their individual health needs, concerns, and goals, the fitness professional can prescribe an exercise program that is safe and effective. The chapter will begin with a discussion of the common treatments for many cancers and their associated side effect and symptom profile relevant to exercise capacity. Next, the need for exercise evaluation and safety considerations will be discussed. Finally, general exercise recommendations for all survivors will be provided with mention of specific programming where indicated and acknowledgement of where there are limitations about what can be recommended at this time.

Side Effects, Symptoms, and Exercise Considerations in the Immediate Posttreatment Period

The overall physical impact of cancer on a patient's quality of life is highly dependent upon the treatment regimens the person undergoes. Cancer treatment varies according to the cancer type, stage, and other factors. Multiple treatment types may be used in combination, which increases the cumulative toxicity of treatments. For example, sequential administration of surgery, radiation therapy, and chemotherapy is common for early stage breast cancer, followed by antihormone therapy for 5–10 years [32]. Thus, the survivor may experience a combination of symptoms and side effects specific to each type of treatment and/or an additive effect from multiple types of treatment that produce the same side effect, such as fatigue. The most common cancer treatments include the following:

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- *Surgery*. Some cancers are removed by surgery (also called resection). Though typically performed with scalpels or lasers, other techniques involve the destruction of cells with extreme cold (cryosurgery) or heat (hyperthermia). Reconstruction surgery may also be performed after surgical debulking of the tumor and any subsequent adjuvant treatments are completed; thus the fitness professional should be aware of the potential for a survivor to face additional surgeries in the immediate posttreatment period.
- *Chemotherapy*. This treatment involves the use of powerful medications to kill rapidly dividing cells in the body or slow their rate of growth. Cytotoxic chemical drugs disrupt the life cycle of cancer cells by damaging DNA or disrupting new DNA creation. Chemotherapy can affect both cancer and normal cells. Chemotherapy is used in early stages before surgery to shrink the tumor (neoadjuvant) and after surgery (adjuvant) or by itself in advanced stages.
- *Radiotherapy*. This treatment involves high doses of ionizing radiation that are directed specifically at the tumor or, following surgery, to the area where cancer occurred. High-energy x-rays are used to damage DNA in cancer cells by either killing or stopping new cancer cells from being made. The most common method

used is external beam radiation therapy, where conformal techniques shape the radiation dose to the cancer site to spare healthy tissue. Radiation damages and eventually destroys rapidly dividing cells in the targeted region of the body, and when these are non-cancer cells, their lifespan and functionality can be impaired.

- *Antihormone therapies*. These treatments are aimed at reducing sex steroid levels in cancers where tumor growth can be fueled by estrogen or testosterone. Treatments can include those which disrupt the hypothalamic-pituitary-gonadal axis (e.g., GnRH agonists), interrupt the synthesis of sex steroids, or block hormone receptor binding.
- *Immune therapies*. These treatments involve the use of monoclonal antibodies, vaccines, or bacteria to stimulate immune or other mechanisms to act against cancer cells.
- *Targeted therapies*. These emerging treatments target tumor-specific driver mutations that are critical for the growth/survival of tumor cells, and such treatments have demonstrated improved survival [23]. Targeted therapies are used in advanced stage diagnoses, though a driver mutation with an associated targeted therapy must be identified for this treatment to be utilized.

Even if treated for the same type of cancer, cancer survivors vary in the nature and pattern of their responses to treatment. Even in the same patient, some side effects might subside within a short time after treatment is completed, others might gradually subside over many months, yet others might persist for years and potentially a lifetime. Given this variability in the nature and trajectory of cancer-related sequelae, individual consideration of conditions that might impact a person's safety and tolerance for exercise is strongly recommended. A thorough review of medical records (if accessible), a comprehensive client intake process, and performance assessment are advised.

The goal of cancer treatment is complete remission, meaning that the signs and symptoms of the disease have disappeared. Even after several years of remission, cancer can return, or the original treatments can produce adverse effects; thus, cancer survivors are often monitored for many years after active treatment ends. Fitness professionals need to obtain as much information as possible about the treatments a cancer survivor has received and to research the immediate and long-term adverse effects of those treatments prior to evaluation and exercise prescription. Contact with the cancer treatment team would be appropriate for this purpose. The oncology clinical team is focused on cure. As such, they may not communicate extensively about immediate and long-term adverse treatment effects. Fitness professionals may therefore find that they are the first to discuss with the survivor these effects of treatment, which is important to do because they can influence exercise tolerance.

Next, we describe the most common cancer treatment-related side effects and symptoms that may impact exercise tolerance but which also may be a health outcome that could be improved with exercise. Since some side effects and symptoms are common across many treatments (i.e., fatigue); those will be discussed first and then followed by the side effects and symptoms that tend to be more specific to a particular type of treatment (i.e., chemotherapy-induced peripheral neuropathy).

Table 12.1 Side effects of cancer treatments and associated exercise limitations

Therapy type	Symptoms and side effects	Exercise limitations
Surgery	Fatigue Muscle weakness Psychosocial distress Pain Lymphedema Limited ROM	ROM, pain, and inflammation at the surgical site may limit exercise movements Perceived fatigue may be increased by medications for pain relief in the immediate postsurgical time period.
Radiation therapy	Fatigue Muscle weakness Psychosocial distress Pain Lymphedema Limited ROM	ROM, pain, and inflammation at the radiation site may limit exercise movements. Fatigue may increase with the cumulative number of radiation treatments completed.
Chemotherapy	Fatigue Muscle weakness Psychosocial distress Pain Neurotoxicity Neuropathy Cognitive difficulties Vestibulotoxicity Ototoxicity Cardiotoxicity	Neuropathy may increase fall risk due to balance/gait changes Altered fine motor skills may affect use of equipment (i.e., gripping hand weights). Hearing loss and cognitive trouble can limit ability to follow/retain exercise instruction Low initial cardiorespiratory fitness may limit intensity and duration of aerobic exercises.
Hormone therapy	Fatigue Muscle weakness Psychosocial distress Pain (arthralgia, myalgia) Altered body composition (↑fat mass, ↓lean mass, ↓bone density) Cognitive difficulties Vertigo Hyperlipidemia Hypercholesterolemia Frailty	Low initial fitness Potential fall risk due to weakness and instability Risk of fracture in those with low bone mineral density.

ROM range of motion

Typical treatments for cancer, their associated symptoms and side effects, and potential limitations to exercise are summarized at the end of this section in Table 12.1.

Common Side Effects Across Cancer Types and Treatments

Fatigue Fatigue is the most common side effect during cancer treatment. Over 90% of patients experience fatigue during treatment, and in as much as 60% of survivors, fatigue will persist after treatment has ended [49]. Cancer-related fatigue is distinct from the tiredness that the average person feels at the end of a work day or after a long exercise session and is described as feeling "sick". The experience of

cancer-related fatigue has been associated with elevated cytokines; however, whether it is centrally or peripherally mediated remains unclear, and the precise mechanisms may vary across individuals, treatments, and time. Fatigue is a side effect that can linger long after treatment ends and may be complicated and confounded by other side effects from cancer treatment or other comorbid conditions such as hypothyroid, cardiac dysfunction, or depression. Universally, the impact of persistent fatigue could manifest as a reduced exercise tolerance and potentially reduced motivational drive. Thus, adjusting the exercise prescription to an individual's symptom level may improve compliance. Baseline assessment should include measures of functional capacity, muscle strength, and exercise tolerance to provide an individually tailored exercise prescription. To maintain effectiveness yet accommodate day-to-day fluctuations in fatigue levels, training programs should have both progression and flexibility for modifications built in [53]. Regular symptom-limited exercise can be an effective countermeasure for treatment-related fatigue. Research has clearly demonstrated the benefits of aerobic exercise and/or resistance for reducing fatigue [2, 22, 26, 28] and demonstrated that fatigue reductions get better as the duration of training is lengthened to longer than 30 minutes per session; however a cumulative dose beyond 150 minutes per week of aerobic exercise may not result in any greater reductions in fatigue. To increase adherence, survivors should be encouraged to select activities they enjoy.

Muscle Weakness Muscle weakness is a common side effect of cancer treatment that is usually associated with inactivity and associated debilitation. Early studies suggest that some forms of muscle weakness may be related to anthracycline (e.g., doxorubicin) treatment, a type of chemotherapy. Studies examining the effects of doxorubicin suggest that skeletal muscle weakness and dysfunction may be induced by oxidative stress, similar to the effects this drug has on cardiac muscle [10, 15, 20, 35]. In a study of breast cancer survivors assessed after the completion of primary chemotherapy, muscle strength was 20–30% lower in seven different exercises when compared with cancer-free controls [16]. Androgen deprivation therapy (ADT), which is commonly used as treatment for prostate cancer, results in an abrupt loss of lean body mass accompanied by a reduction in muscle strength and endurance [11, 14]. Since most cancer survivors are older when diagnosed, treatment may compound age-related weakness and sarcopenia. For patients with any degree of muscle weakness, the fitness professional should tailor the exercise programs to each person's relative capacity and progress the program gradually. Resistance training may be a particularly important modality; moreover, exercises that focus on functional movements should be considered. In some contexts, such as the absence of the anabolic drive from testosterone in the setting of ADT or survivors who received full mantle radiation, resistance training may not build lean mass. However, neuromuscular contributions (i.e., maximal motor unit firing rates or neuromuscular activation) explain some of the variation in muscle strength in older adults [1, 3, 36, 55]; thus resistance training may still effectively improve muscle strength in the absence of gains in muscle mass [51].

Pain Cancer-related pain is an unpleasant sensory and emotional experience that is most commonly a consequence of the malignancy [29]. The complex and variable types of pain are dependent on the stage of disease and/or treatment. Pain is common in persons with metastatic disease but can also result from surgery, radiation therapy, chemotherapy, and antiestrogen hormonal therapies. Cancer that has spread to the bones is often painful, and bone pain can be an initial sign of skeletal metastases. Exercise training may be safe and tolerated in persons with skeletal metastases when it is carefully prescribed and limits or avoids involved skeletal sites [6]; however, there is much to be learned about appropriate exercise in the metastatic setting, and fitness professionals should reduce risks of fracture as much as possible. Pain related to surgery or radiation therapy is mostly localized to the treatment site and could limit a person's tolerance for exercises using the involved or proximal joints and musculature. Survivors may be able to exercise with pain that is tolerable and not worsened by exercise; however, modification or omission of individual exercises that exacerbate pain may be necessary. For persons treated with chemotherapy, pain associated with peripheral neuropathy may also linger and impact mobility and function of both the lower and upper extremities [47]. Arthralgias (joint pain) and myalgias (muscle pain) are common side effects of aromatase inhibitor therapy for breast cancer and may limit exercise tolerance.

While exercise may need to be modified to accommodate pain and improve compliance, exercise may also be an effective therapeutic strategy to reduce chronic musculoskeletal pain. In a randomized controlled trial of previously inactive breast cancer survivors, a yearlong program of combined moderate-intensity aerobic and resistance training was well tolerated and significantly decreased joint pain, pain severity, and pain interference [19]. In head and neck cancer survivors, progressive resistance training reduced shoulder pain and reduced upper extremity disability [27].

Psychosocial Distress Cancer and its diagnosis can cause significant distress to the patient and his/her loved ones, particularly caregivers. For some people, the emotional toll of cancer is severe enough to lead to post-traumatic stress disorder. Others don't quite reach the level of clinical syndromes but still have significant worries, fears, and other psychological sequelae. For example, a working mother who had a mastectomy for stage 3 breast cancer might experience distress around body image, fears of cancer recurrence, and worries about her ability to return to work or care for her children. The emotional stress and strain of cancer do not evaporate once treatment is over. In fact, the transition from oncological care back to the primary care setting can be a very difficult time psychologically for patients and families because there are few resources or systems to help people navigate back to their everyday lives.

Exercise, which is known to help reduce depression and anxiety and elevate mood, is beneficial for someone with a history of cancer [7]. Regular aerobic exercise, with or without added resistance training, appears to be the most effective modality of exercise training to reduce anxiety and depression and may be more

beneficial as training sessions lengthen and are delivered in a supervised setting [2, 22, 26, 28]. Interestingly, resistance exercise alone does not yet appear to effectively improve mood in cancer survivors for reasons that are not entirely clear. Since a cancer diagnosis and lingering side effects, like cognitive difficulties, can socially isolate a cancer survivor from others, group exercise with other cancer survivors may be an effective way to re-engage and energize a client. However, it is important to recognize that psychological distress, in its many forms, may also impact a cancer survivor's self-efficacy, confidence, motivation, and willingness to begin an exercise program, in addition to his/her ability to stick with this lifestyle change over time. When working with cancer survivors, the fitness professional should be aware of the emotional burden caused by cancer, particularly when setting short- and long-term behavioral goals. Additional support and reinforcement may be necessary to improve adherence to a program. Even former athletes may experience frustration getting back to an exercise routine, because their expectations and self-image before cancer may be not match to their current abilities. Overall, fitness professionals should be aware of and respectful of the fact that individuals diagnosed with cancer commonly have many concerns, such as life expectancy, employment issues, and family matters that may limit prioritization of exercise in their lives.

Side Effects More Common to Surgery and Radiation

Lymphedema Lymphedema is a common sequelae of surgery and sometimes radiation therapy and results from removal and/or damage to lymph vessels and nodes. Disruption of the lymphatic system can weaken its ability to properly clear lymph fluid from surrounding tissues, causing fluid to build up in the affected areas. For example, upper limb lymphedema can occur in 10–90% of breast cancer survivors who are treated with surgery and/or radiation therapy [17]. The onset of lymphedema can vary and may even manifest several months or longer after treatment completion. Lymphedema is not a contraindication to exercise. Rather, resistance training may be helpful in restoring normal lymph function in affected limbs. However, exercise must be carefully approached to avoid exacerbation of symptoms. A program should begin at a low intensity and progress slowly, and the fitness professional should monitor the patient for exacerbation of symptoms (e.g., increased swelling or pressure in the affected limb). Since research and guidelines for exercise in persons with lower-extremity lymphedema are less abundant, similar safety precautions should be taken, and symptoms should be aggressively tracked. This topic is covered in greater depth in Chap. 13.

Limited Range of Motion Range of motion (ROM) is often limited as a result of scarring that follows surgical resection of cancer and, in some cases, after radiation therapy. There may be imbalances and weakness after surgical recovery and multiple periods during which exercise is not possible. In particular, survivors of breast and head and neck cancers are often faced with considerable arm and shoulder

morbidity that can limit upper extremity function. Radiation exposure may result in fibrotic sclerosis on exposed nervous tissues, resulting in pain, sensory loss, and weakness. Indirectly, prolonged deconditioning could limit joint mobility. Limited ROM can affect a survivor's ability to fully participate in exercise, particularly resistance training, and thus improving ROM and correcting asymmetries may be an important initial goal of training. Flexibility exercise or low-intensity dynamic exercise, such as water aerobics or tai chi, may improve range of motion even in persons who are many years past treatment completion [21, 30, 31]. Some exercises that are too painful or can never be performed properly may need to be omitted from a training program, and alternative movements are prescribed when possible.

Side Effects More Common to Chemotherapy

Neurotoxic Symptoms Cancer survivors may have been treated with a chemotherapy agent (e.g., platinum-based agents, vinca alkaloids, taxanes) that affects the central and peripheral nervous systems and results in neurotoxicity. Specific sequelae could include ototoxicity, vestibulotoxicity, cognitive difficulties, and/or peripheral neuropathy. Hearing loss and/or cognitive difficulties can affect survivors' ability to hear and follow exercise instructions, especially those involving complex movement sequences. Vestibulotoxicities are difficult to identify but may manifest as vertigo, unsteadiness, or chronic dizziness. As such, safety precautions to reduce fall risk during exercise should be identified and implemented.

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting side effect of treatment with drugs, such as platinum drugs, taxanes, epothilones, vinca alkaloids, bortezomib, and lenalidomide. CIPN results from damage to peripheral nerves and causes symptoms of numbness and/or tingling in the hands and/or feet that is often painful. CIPN affects anywhere from 20% to 95% of cancer patients, depending on the type chemotherapy, demographic characteristics of the patient, and comorbid conditions. There may be a disproportionate burden of CIPN among older cancer patients [44]. CIPN can interfere with fine motor skills and cause pain and problems with balance and fine motor function, such as descending stairs or buttoning a shirt [18]. CIPN may persist after treatment ends and possibly for many years in as much as 50% of people treated with chemotherapy and is associated with altered gait, reduced physical functioning, falls, and disability [52]. In individuals with CIPN, exercise may need to focus on restoring normal gait and functional mobility while attending to safety precautions that minimize the risk of falls.

When prescribing exercise for survivors with peripheral neuropathy, it is important to consider the deficits in sensory and motor function. Survivors with CIPN may not feel steady on their feet and may also have difficulties holding on to certain types of resistance training apparatus. For a survivor who experiences CIPN that makes walking difficult, recommending exercises that are non-weight bearing (e.g., swimming, stationary bicycling, or rowing) may be feasible options to safely begin

aerobic activity or at the least ensure that weight-bearing activities are safe, e.g., treadmill with handrails. Selecting free weights or therapy bands with soft padded handles or loops may facilitate grip for resistance training. While exercising survivors with CIPN should be advised to wear properly fitting, comfortable closed-toed shoes without heels, inspect shoes for foreign objects prior to putting them on and inspect feet for injury every day and protect hands from cold weather if exercising outdoors. Balance and gait exercises are important to incorporate into an exercise program for survivors with CIPN, particularly exercises that focus on improving sensorimotor function. Since fall risk and balance problems are hallmark to CIPN, it is important that appropriate safety precautions are embedded into balance and gait training programs.

It is not well understood if exercise will alleviate neurotoxic symptoms and side effects. Despite this, exercise training in persons with neurotoxicity is not contraindicated, especially if safety and tolerability are monitored. Exercise is emerging as a possible intervention to reduce peripheral neuropathy symptoms among survivors [9, 54], via the potential to improve motor and sensory function, as well as reduce inflammation and neuropathic pain [9]. EXCAP is a large multicenter randomized controlled walking and resistance exercise trial to prevent CIPN symptoms. In this trial, CIPN symptoms of hot/cold, numbness, and tingling in hands and feet were reduced in the exercise group compared to the control, and the exercise group increased physical activity and muscle strength [24]; however, the intervention was relatively short (i.e., 6 weeks), and thus the sustainability of exercise benefits is unknown. Other types of interventions using novel types of exercise to reduce CIPN symptoms and/or balance problems, including sensorimotor training, whole-body vibration, and interactive sensor-based balance training, are being explored as specific therapeutic interventions [43, 46].

Cardiotoxicity Cardiotoxicities are negative alterations to the cardiac system that may lead to clinically significant cardiac events (i.e., decline in left ventricular fraction, congestive heart failure). In a meta-analysis of 55 published studies reporting early and late cardiotoxic factors associated with anthracycline-based chemotherapy among patients treated for breast or ovarian cancer, lymphoma, myeloma, or sarcoma [45], the risk of increased clinical cardiotoxicity increased fivefold compared to non-anthracycline-based chemotherapy agents. A more detailed discussion of exercise and cardiotoxicity is discussed in Chap. 14, but the key point is that cardiac risks should be considered when developing exercise programming for cancer survivors with a history of chemotherapy.

Side Effects More Common to Antihormone Therapy

Antihormone therapy for breast or prostate cancer aims to reduce sex steroid (i.e., estrogen and testosterone) levels that can drive tumor growth. In breast cancer survivors who are premenopausal at diagnosis, ovarian suppression to reduce circulating

estrogens may be part of primary treatment and may result in permanent ovarian failure in a proportion of women. Antihormone therapy is given to women with estrogen receptor-positive breast cancer after completion of primary treatment (i.e., surgery, radiation, and/or chemotherapy). Women are treated either with a selective estrogen receptor modulator (SERM) or an aromatase inhibitor (AI) and often stay on this treatment for 5–10 years. Side effects of SERMs or AIs that may affect exercise tolerance include fatigue, muscle and joint pain, cognitive difficulties, weight gain, and bone loss. Antihormone therapy for prostate cancer, often termed androgen deprivation therapy (ADT), can be given for prescribed periods of time in conjunction with other treatments or for longer periods of time when cancer is progressing or advanced. ADT can include orchiectomy (i.e., removal of testes), injections with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists to stop the gonads from making testosterone, or oral medications that inhibit the pathways involved in testosterone synthesis or the binding of testosterone to androgen receptors (anti-androgens). Side effects of ADT that may affect exercise tolerance include fatigue, anemia, cognitive difficulties, vertigo, muscle and bone loss, fat gain, hyperlipidemia and hypercholesterolemia, and depression [12]. Breast and prostate cancer survivors who have been treated with antihormone therapy may be more likely to develop osteoporosis, frailty (exhaustion, slowness, weakness, sarcopenia, and inactivity), diabetes, and cardiovascular disease than women and men who don't receive this treatment possibly even if they discontinue therapy [50]. These latter health concerns are covered in more detail in the next chapter.

Other Biologic Therapies: Targeted and Immunotherapy

An emerging and highly studied class of drugs, targeted therapies, block driver mutations (i.e., epidermal growth factor receptor (EGFR) amplifications and anaplastic lymphoma kinase (ALK) translocations) that contribute to cancer cell growth. These therapies have demonstrated improved survival [23]. Targeted therapies are used in advanced stage diagnoses, though a driver mutation with an associated targeted therapy must be identified for this treatment to be utilized. Immunotherapy is a quickly emerging class of drugs aimed at harnessing and enhancing the body's innate and adaptive immune response system activity to destroy cancer cells and is mostly commonly focused on the cytotoxic T-lymphocyte protein 4 (CTLA-4) and programmed cell death protein ligand 1 (PD-L1) pathways. Currently four immunotherapy agents have reached clinical practice, with many more checkpoint inhibitors currently being studied [25].Though there are early reports of high levels of fatigue and endocrine-related immune system adverse events [48], unfortunately the side effect profile of these new classes of cancer treatments is largely unknown. Thus, the fitness professional must continually seek information that could help inform the safety and efficacy of exercise for their clients who are treated with these newer agents.

Exercise Programming Considerations in the Immediate Posttreatment Period

Since cancer survivors are often older at diagnosis and since cancer treatment can alter cardiorespiratory and metabolic health, it is important to consider whether or not cancer survivors require medical clearance (i.e., approval from a medical professional to engage in exercise) prior to starting an exercise program. Current American College of Sports Medicine (ACSM) pre-participation exercise guidelines for all persons aim to reduce barriers to exercise by removing a requirement for medical clearance for individuals whose risk of an adverse cardiac event during exercise is low, including exercise naïve persons [37]. These ACSM pre-participation guidelines should be applied in cancer survivors to minimize risks of adverse exercise-related events; however, these ACSM guidelines do not explicitly address risks for adverse events and/or injury during exercise that are specific to the side effects of cancer treatment. We refer the fitness professional to the recently updated ACSM exercise guidelines for cancer survivors that frame recommendations for when medical clearance and/or further medical evaluation by a medical professional is indicated, as well as the level of supervision during exercise training for cancer survivors to ensure safety based on the disease and treatment-related side effects (Table 12.2).

There is a range of levels of function and ability to exercise among those who have been treated for cancer. Further, cancer is diagnosed at many ages, in people that vary broadly with regard to their exercise and health histories. The challenge is to get as many cancer survivors as possible active while avoiding unnecessary risk to them. Ideally, cancer survivors should receive a comprehensive assessment of all components of health-related physical fitness (i.e., cardiorespiratory fitness, muscle

Table 12.2 Adapted National Comprehensive Cancer Network triage approach based on risk of exercise-induced adverse events

Description of patients	Evaluation, prescription, and programming recommendations
No comorbidities	No further pre-exercise medical evaluation∗ Follow general exercise recommendations
Peripheral neuropathy, arthritis/ musculoskeletal issues, poor bone health (e.g., osteopenia or osteoporosis), lymphedema	Recommend pre-exercise medical evaluation∗ Modify general exercise recommendations based on assessments Consider referral to trained personnel[a]
Lung or abdominal surgery, ostomy, cardiopulmonary disease, ataxia, extreme fatigue, severe nutritional deficiencies, worsening/changing physical condition (i.e., lymphedema exacerbation), bone metastases	Pre-exercise medical evaluation∗ and clearance by physician prior to exercise Referral to trained personnel[a]

Legend: [a]Rehabilitation specialists (i.e., physical therapists, occupational therapists, physiatrists) and certified exercise physiologists (i.e., ACSM-CEP, CSEP-CEP, ESSA-AEP)
∗Medical evaluation—per NCCN guidelines for specific symptoms and side effects

strength and endurance, body composition, and flexibility), with some specific cancer-specific considerations, as recommended in the ACSM exercise guidelines for physical activity in cancer survivors (Table 12.3), in order to individualize an exercise prescription. However, requiring a comprehensive physical fitness assessment prior to starting exercise may create an unnecessary barrier to starting activity. For this reason, no assessments are recommended prior to start low-intensity aerobic training (i.e., walking or cycling), resistance training with gradual progression, or a flexibility program in most survivors [2].

Fitness professionals should be prepared to create exercise programs that meet the survivor's needs. A customized program may not yet resemble or reach the exercise programs recommended in current guidelines [5, 39, 42], such that a goal may be to strive toward preparing the survivor to engage in recommended types and levels

Table 12.3 Exercise testing recommendations

Standard exercise testing methods are generally appropriate for patients with cancer who do not require medical clearance or who have been medically cleared for exercise with the following considerations:
Be aware of a survivor's health history, comorbid chronic diseases and health conditions, and any general exercise contraindications before commencing health-related fitness assessments or designing the exercise prescription.
Be familiar with the most common toxicities associated with cancer treatments including increased risk for fractures and cardiovascular events, along with neuropathies or musculoskeletal morbidities related to specific types of treatment.
Health-related fitness assessments may be valuable for evaluating the degree to which components of fitness have been affected by cancer-related fatigue or other commonly experienced symptoms that impact function [26].
In principle, there is no evidence that the level of medical supervision required for symptom-limited or maximal cardiopulmonary exercise testing needs to be different for patients with cancer than for other populations [37].
The evidence-based literature indicates that 1-RM testing is safe among survivors of breast and prostate cancer without bony metastases [41].
Among patients with bony metastases or known or suspected osteoporosis, routine assessments of muscle strength and/or endurance involving musculature that attaches to and/or acts on a skeletal site that contains bone lesions should be avoided [13]. For example, 1-RM testing for leg strength (e.g., leg press) should be avoided in patients who have bony metastases in the proximal femur (i.e., hip) or vertebrae. Other sites where lesions are absent could be tested. In this example, if the patient had no lesions in the upper body, 1-RM for a chest press or 1-RM for a seated row might be feasible, given no other contraindications. Medical clearance from a physician (i.e., orthopedic or radio-oncology) may be mandatory depending on the scope of practice or protocols at a specific site/facility.
Older survivors and/or survivors treated with neurotoxic chemotherapy (typical for breast, colon, lung, and ovarian cancers) may especially benefit from a standard assessment of balance and mobility to assess fall risk [33].
CVD has become a competing cause of morbidity and mortality for survivors of cancer with a favorable prognosis [34]. Given the potential for underlying CVD, cancer survivors should be screened for evident or underlying CVD using the ACSM pre-participation guidelines and if implicated have a cardiopulmonary exercise test prior to beginning an exercise program [38].

of exercise over their lifetime as outlined in the 2018 Physical Activity Guidelines for Americans [4]. The fitness professional should monitor for early signs of poor tolerance to training and adjust the dose of exercise accordingly even if this means dropping below recommended training volumes. The fitness professional is further urged to collaborate with and support clinical oncology specialists to help clients avoid inactivity, maintain normal daily activities, and improve outcomes after treatment and beyond. For example, it is possible that at the end of their primary treatment, survivors have significant toxicities, impairments, and limitations that prevent them from working toward recommended levels of exercise. These types of survivors should be referred to a physical or occupational therapist to correct problems with a goal to enable the survivor to engage in routine exercise training.

Prescribing Exercise in the Immediate Posttreatment Period

The recently updated ACSM exercise guidelines for cancer survivors issued evidence-based exercise prescriptions for outcomes where there was sufficient science to do so [2, 22, 26, 28]. Only traditional modalities of exercise training were considered, e.g., aerobic training, resistance training, or combined aerobic and resistance training, since the evidence base for less traditional or novel types of exercise training, such as yoga, high-intensity interval training, etc., was either inconsistent or immature. Currently, the exercise prescription that most consistently addresses health-related outcomes experienced due to a cancer diagnosis and cancer treatment includes moderate-intensity aerobic training at least three times per week, for at least 30 minutes, for at least 8–12 weeks. The addition of resistance training to aerobic training (20–30 minute/session), at least two times per week, using at least two sets of 8–15 repetitions at least 60% of 1 repetition maximum, appears to result in similar benefits (Table 12.4). Resistance training only programs are also efficacious at improving most health-related outcomes, though in a few instances the evidence is either insufficient or shows no benefit (e.g., depressive symptoms). While in most cases benefits were derived from exercise delivered in a supervised or home setting, benefits tended to be greater among supervised exercise programs. Additional types of exercise training, such as flexibility exercise and balance and gait training, may certainly be appropriate modalities to incorporate into an exercise

Table 12.4 Expected patient benefits from exercise training by mode

Aerobic	Resistance	Aerobic plus resistance
Reduced anxiety Fewer depressive symptoms Less fatigue Better QoL Improved perceived physical function	Less fatigue Better QoL No risk of exacerbating lymphedema Improved perceived physical function	Reduced anxiety Fewer depressive symptoms Less fatigue Better QoL Improved perceived physical function

program that meets a survivor's needs and should be considered at the discretion of the fitness professional. For example, a restorative yoga program that consisted of a series of stretching exercises reduced fatigue and increased readiness to work toward meeting current public health physical activity recommendations in breast cancer survivors either during or soon after treatment [53]. A companion paper to the ACSM exercise guidelines for cancer survivors further addresses how clinicians can implement these recommendations and discusses additional programming considerations, such as exercise setting [40].

Summary

The immediate posttreatment period can be a challenging time to prescribe exercise for a cancer survivor just finishing one or more of the aggressive treatments for cancer. The physical and emotional toll of a cancer diagnosis and subsequent treatments can be profound and cause side effects and symptoms that limit a survivor's exercise ability and tolerance. However, it can also be an opportune time for a survivor to consider making an important behavioral change to a more physically active lifestyle since they may now better appreciate the potential benefits to their quality of life and longevity. Exercise can also play an important role in the survivor's recovery because it can lessen or ameliorate many of the side effects and symptoms that linger after treatment. To effectively and safely program exercise in the immediate posttreatment period, the fitness professional must know the treatment(s) he/she has received and what limitations this may present for their exercise program. In general, a moderate-intensity aerobic, resistance, or combined aerobic and resistance exercise training program, performed at least three times per week for at least 30 minutes per session, can improve many health-related outcomes for cancer survivors. Whether or not medical clearance and/or a pre-exercise medical evaluation is necessary depends on the initial health history of the survivor. Ideally an initial fitness evaluation would be performed to guide the fitness professional about how to best design a tailored exercise program that meets the needs, abilities, and preferences of their client.

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Chapter 13
Long-Term and Late Effects of Cancer Treatments on Prescribing Physical Activity

Anna L. Schwartz, Jennifer W. Bea, and Kerri Winters-Stone

Overview of Long-Term and Late Effects

As survivors move through the survivorship trajectory, prescribing physical activity changes from focusing on acute disease and treatment-related side effects to improving functional ability and maximizing quality and quantity of life. Exercise and physical activity are vital in maintaining and improving health for long-term survivors. As cancer survivors transition out of active treatment, care must focus on health promotion and disease prevention. As such, it is vital for exercise professionals to understand the long-term and late effects of cancer and how they influence physical activity prescription.

Long-term cancer survivors may be faced with unique health concerns that linger many months after treatment ends (long-term effects) or that develop many years after treatment (late effects). Structured rehabilitation, including regular physical activity and exercise, should be at the forefront of survivorship and should be individualized to each survivor's ability and immediate and long-term goals [1, 2]. However, each form of treatment a survivor undergoes presents unique long-term and late side effects that will influence the optimal settings (e.g., supervised, group, home-based) to gain the best positive physical and emotional outcomes [3–5]. The decision to choose a clinically supervised versus community- or home-based exercise program should be determined by the degree of compromise or function of the survivor, their previous experience with exercise, and their personal preference(s). When developing a prescriptive exercise program, it is important to consider

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long-term effects the survivor may experience. Some of these long-term and late effects include fatigue, frailty, quality of life, bone loss, and falls, as well as cardiac, pulmonary, endocrine, and immune problems. Specific exercises may need to be adapted to accommodate individual limitations to maximize the potential benefits of exercise.

Distinct and unique late effects of treatment may pose health challenges that necessitate modifying an exercise regimen for cancer survivors. Developing exercise prescriptions for long-term survivors requires an understanding of not only the survivor's type and stage of cancer and treatment regimen(s) but also other comorbid conditions which may impact their ability to exercise. These comorbid conditions include such common diseases as hypertension, cardiac arrhythmias, chronic obstructive pulmonary disease, asthma, diabetes, osteoporosis, and diseases of aging such as cognitive decline, cerebrovascular attack, essential tremors, or Parkinson's. While a discussion of these individual disorders is beyond the scope of this chapter, an understanding of how the different impairments and limitations resulting from various comorbid conditions may compound the late effects of cancer is paramount in developing safe and effective physical activity prescriptions. However, exercise has been shown to improve each of these conditions as well, so there is no reason not to begin and progress in an exercise program. The frequency, intensity, time, and type (FITT) of activity at the starting point and rate of progression simply need to be considered based on the type and stage of cancer, treatment regimen(s), presence and severity of long-term and late effects, and other comorbid conditions.

An example of how cancer-related side effects may intersect and be influenced with other side effects is fatigue. Fatigue is made worse when long-term survivors must also cope with concurrent late effects, such as peripheral neuropathy, Raynaud's phenomenon, hypothyroid disease, physical declines from aging and debilitation, anxiety, and depression. Many long-term survivors are physically debilitated from a sedentary lifestyle that not only worsens fatigue, muscle weakness, and risks for falls, but undoubtedly contributes to depression and anxiety. Exercise and physical activity can mitigate many of these long-term and late effects of cancer treatment, but it is important to prescribe an exercise program that is structured to progress slowly in a step-by-step fashion to avoid injury, worsening of fatigue, or creating an exercise prescription that is too challenging, which may result in a survivor becoming disheartened and eventually quitting the exercise program.

Goals of Exercise Programming

The goal of exercise programming after treatment is to optimize recovery of physical functioning to a level that enables the survivor to engage in activities of daily living, to participate in activities that are meaningful, and to help return to full function [6]. At every visit, whether in an oncology clinic or primary care office, clinicians

(e.g., physicians, nurse practitioners, nurses, physician's assistants) should inquire and provide advice to exercise and referral to an appropriate program (clinically supervised or community-based), and at subsequent visits, the provider should ask follow-up questions to assess engagement in exercise, progress toward increasing physical activity, and effects or benefits the survivor reports. If the provider does not feel competent to provide exercise advice, referral to an exercise professional in a clinically based program or supervised community-based program is appropriate and necessary.

While the majority of survivors can safely exercise in the community by participating in programs such as LIVE**STRONG** at the YMCA, MoveMore program, or following a home-based exercise program, survivors with multiple side effects from treatment that limit function, those who are significantly debilitated, or those who have serious compounding comorbidities may require referral to a clinically supervised exercise program. These programs are commonly located in medical settings such as inpatient, outpatient rehabilitation, primary care, and palliative or hospice care and have a healthcare professional (e.g., physical therapists, occupational therapists, clinical exercise physiologists, physiatrists) overseeing the exercise program. The decision to refer a survivor to a clinically supervised exercise program or a community-based program should be determined by their functional ability, current medical condition, prior history of exercise, preference, and availability of programs. Over time, and with good adherence to a structured, progressive clinically based exercise program, most survivors who initially need a supervised clinically based exercise program can progress and transition to a community- or home-based exercise program.

To prescribe a safe and effective exercise program, the cancer survivor's exercise tolerance must be assessed. It is also important to understand the type and extent of cancer a survivor had or has, and the type(s) and duration of treatments, as this will influence the number and severity of possible side effects they are at risk of experiencing. Exercise tolerance may vary due to the effects of cancer treatments and treatment-related side effects [7] and effective exercise prescriptions may need to focus on improving the area of greatest impairment [8]. Regular assessment of survivors in clinically supervised exercise programs is important to not only assess progress but to adapt and revise the program as needed to accommodate changes in the survivors' functional ability, side effects, etc. Assessment will also guide the clinician and exercise professional in determining when the survivor is ready to transition to a community-based exercise program [9–11].

Whether a survivor is exercising in a clinically supervised exercise program or in the community setting, it is critical to have a strong understanding of the long-term and late effects of cancer that may impact and necessitate modifications to an exercise program. Every encounter should include an assessment of how the survivor is feeling, how s/he felt after the last exercise session and an assessment of their short- and long-term goals. This rapid assessment should guide the next exercise session and any adaptations to the exercise prescription that might be needed.

Exercise Prescription

An effective exercise prescription for cancer survivors must be one that is tolerable and does not exacerbate side effects of treatment and other symptoms. The exercise prescription should be based on FITT (frequency, intensity, time, and type), as noted above, and adjusted or adapted as needed by the survivor.

The minimum exercise prescription should include moderate-intensity aerobic exercise at least 3 times a week for at least 30 minutes. Resistance exercise should focus on strengthening large muscle groups and be performed at least 2 times a week doing at least 2 sets of 8–15 repetitions focusing on large muscle groups [12]. For survivors who are too debilitated to begin with this minimal FITT prescription, the exercise FITT should gradually increase as tolerated by the survivor who may need to perform several short bouts of exercise over the day to develop the aerobic capacity and strength to engage in longer periods of exercise.

It is important to remember that intensity is relative. For example, "moderate" intensity for a young, fit survivor will be of a higher absolute intensity than for a debilitated or older cancer survivor. Teaching the cancer survivors how to assess their own intensity level is an important step that can be covered during goal setting. Intensity can be measured in many ways, such as target heart rate, but often, the most memorable way to help someone tune into their personal intensity levels is the simplest. You can teach clients the "talk test" by using the following rules, as a general guide.

- Low intensity: You can sing
- Moderate intensity: You can talk, but not sing
- High intensity: Talking becomes more difficult and you speak in broken sentences between breaths

A slightly more complex guide to relative intensity is the Rate of Perceived Exertion Scale, which can be taught if the client is more familiar with their effort levels, has exercised regularly in the past, or prefers a numbered scale. The Rate of Perceived Exertion Scale provided here (Fig. 13.1) incorporates more detailed information on the ability to talk or carry on a conversation, as well as a numbered scale.

Many cancer survivors can and do engage in regular exercise without approval from their physicians, but for survivors who are significantly debilitated or have multiple comorbidities, physician advice and referral to either a clinically supervised exercise program or a community-based exercise program may be advisable. An example of cancer survivors who may need greater supervision, monitoring or modification to exercise include those with cardiopulmonary disorders (e.g., heart failure), bone metastasis, or even patients who are significantly, physically debilitated or have never engaged in exercise before and do not know how to start or pace themselves. These survivors may benefit from a clinically supervised program prior to transition to an exercise professional-supervised community program, such as LIVE**STRONG** at the YMCA or MoveMore, as the survivor improves their aerobic capacity, muscle strength, and confidence. The following are common long-term

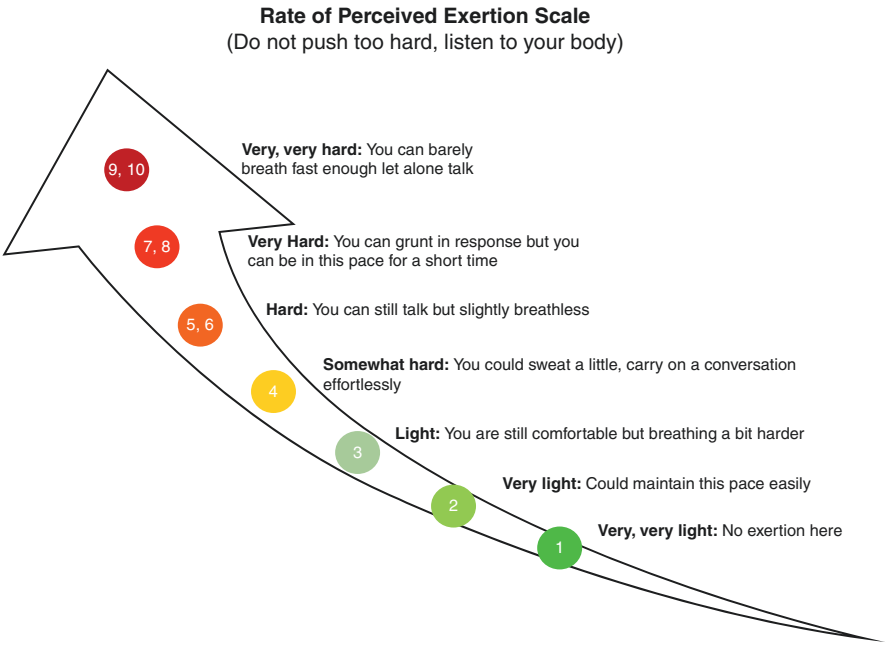

Fig. 13.1 The Rate of Perceived Exertion Scale

and late effects of cancer treatment that may confront the practitioner in developing and modifying exercise programs for cancer survivors.

Lymphedema

Lymphedema is often thought to be an acute side effect of breast surgery, but it can present many years after surgery. Lymphedema may be provoked by excessive stress to the upper extremity, an injury, or even airline travel. Late-onset lymphedema can be just as challenging to the survivor as when it presents early in the cancer trajectory and can cause problems that limit physical activity and lead to a sedentary lifestyle.

Historically, breast cancer survivors were advised to carry "nothing heavier than a handbag" and upper body exercise had been completely discouraged for women who had axillary lymph node dissection or radiation therapy. This antiquated recommendation left women with weak and debilitated arms and a fear that they may develop lymphedema if they did use their arm. This advice may actually have been a precipitating or contributing factor in the development of late-onset lymphedema.

Randomized clinical trials have now conclusively demonstrated that upper body muscle strengthening exercise can be safely performed following the ACSM guidelines [13–15]. Groundbreaking research from the Physical Activity and

Lymphedema (PAL) trial changed the clinical care of breast cancer survivors at risk for lymphedema. This study demonstrated that a supervised, progressive resistance exercise program performed twice a week reduced the risk for lymphedema and lymphedema flares and that neither arm volume nor symptom severity worsened with exercise [16]. It needs to be stressed that the PAL protocol begins with extremely light weights (1 pound) and progresses very slowly (after 2 weeks with that weight). The PAL protocol stresses moving the weight through the full range of motion and using correct form all the way through the exercise. If the survivor is unable to maintain the correct form, then a lighter weight should be used. Exercise guidelines now recommend supervised progressive resistance exercise for breast cancer survivors during and after breast cancer treatment [17–19]. Insufficient evidence exists to determine if unsupervised resistance exercise is safe for women with or at risk for lymphedema.

The PAL program is now a clinical program called Strength ABCs (Strength After Breast Cancer). When delivered in a physical therapy clinic, the Strength ABCs program is paid for by private insurance, Medicare, and Medicaid. The program is initially delivered by physical therapists who have been trained in the protocol and is available at multiple locations. Patients progress to home-based exercise after 6 visits. Professionals wishing to become certified in their own center may register and pay for the required 4-hour online training course. Only licensed physical therapists, occupational therapists, certified athletic trainers, or nationally certified fitness professional with certification specific to working with cancer patients and with access to a Certified Lymphedema Therapist (CLT) are eligible for the training. Another resource is the Strength and Courage: Exercises for Breast Cancer Survivors available on DVD or online download.

Exercise prescription for breast cancer survivors with a history of lymphedema or at risk for lymphedema should include aerobic and resistance exercises. Aerobic exercise may be performed without fear of exacerbating lymphedema, but resistance exercise must be performed and progressed slowly and, ideally, initially under the supervision of an exercise professional with specific knowledge and training in cancer and lymphedema. While there is no conclusive evidence that aerobic exercise will prevent or treat lymphedema, it is beneficial to overall physical and emotional health and therefore highly recommended. Resistance exercise, however, has a clear benefit in reducing risk for lymphedema, flares, and severity of lymphedema and should be prescribed in a slow and progressive manner consistent with ACSM recommendations [12].

Fewer studies have been conducted on lower limb lymphedema; therefore, evidence-based exercise recommendations for the lower limbs lymphedema require further study. Pilot studies provide promising evidence for aquatic training [20] and weight lifting [21]. However, larger trials are needed to confirm safety and efficacy. LIVE**STRONG** at the YMCA recommends large muscle exercises that engage the pelvis, lower extremities to the toes to reduce accumulation of lymph fluid. Some exercises that are used in the LIVE**STRONG** at the YMCA are hip flexes, hip abduction, knee extensions, ankle pumps, ankle circles, toe scrunches, and deep breathing exercises.

Quality of Life

Exercise can improve quality of life for cancer survivors regardless of type of cancer, stage of disease, or type of treatment [22]. Exercise can reduce anxiety, depression, stress, and improve self-esteem, social functioning, and general quality of life [23–25]. Exercise helps survivors to feel physically and emotionally better, function better in their daily lives, and reduce perceived health concerns by focusing on health rather than illness [22].

Exercise prescriptions to improve quality of life will certainly improve other physical aspects of survivorship, if the program is developed in a systematic step-by-step fashion to gradually increase functional ability and muscle strength. Aerobic exercise appears to be more beneficial than resistance exercise to improve quality of life, but a combined aerobic and resistance exercise program (discussed in the section "Exercise Prescription") is recommended to improve quality of life and other aspects of survivorship and health.

Frailty

A growing body of evidence suggests that cancer treatment may hasten the development of frailty and thus place older cancer survivors at a particularly high risk of poor health outcomes. Frailty is the culmination of declines in several physiologic systems and is usually associated with advanced age. Fried et al. proposed five criteria to objectively measure frailty and demonstrated that older adults with at least three of the five frailty criteria (i.e., unintentional weight loss, exhaustion, weakness, slow walking speed, low physical activity) were at increased risk of worsening mobility, hospitalization, and death [26, 27].

The physical problems reported by cancer survivors, such as cognitive difficulty, neuropathy, sarcopenia, muscle weakness, slowing, and fatigue, may be similar to those of older people without cancer, but cancer treatment can worsen these declines such that the trajectory toward frailty begins at an earlier age or is accelerated in an older survivor [28–30]. For example, childhood cancer survivors have an increased prevalence of frailty in adulthood at an age not typically associated with frailty [31]. This increased prevalence of frailty is thought to be due to the effects of cancer treatment. Other studies have reported a higher prevalence and earlier onset of frailty among breast cancer survivors compared to women without cancer [32]. A particularly salient point about frailty is that the cancer exercise professional (CEP) should not assume that the chronological age of survivor is indicative of their "functional" or "biological" age and thus, their baseline exercise capacity and exercise tolerance may be lower than expected for a given age group.

At the very least, a baseline assessment should be performed when possible to determine the survivors starting point for an exercise program. Objective assessment of frailty, though, is within the scope of pre-exercise evaluation [26] and

can also be obtained by self-report if objective assessment is not possible [33]. By detecting frailty early, as a "pre-frail" state, the CEP can help the patient prevent this syndrome. It is also possible to move a patient along the frailty continuum to a lesser state, e.g., from "frail" to "pre-frail." Because inactivity is itself a component of frailty and affects other frailty components, exercise is a reasonable strategy to address this syndrome in any population. Cancer survivors in particular are prone to inactive lifestyles because of the impact of cancer and related treatments; thus, the CEP can play a key role in preventing or reversing frailty.

Bone Loss

Treatment for several cancers can accelerate bone loss, increasing the risk for osteoporosis and subsequent fractures. For example, breast and prostate cancer survivors on long-term hormonal therapies to reduce circulating estrogen or testosterone levels are at an elevated risk of fractures. Thus, the use of exercise to reduce fracture risk, along with appropriate precautions and modifications, should be a central consideration.

Several research studies have aimed to determine whether exercise can slow bone loss in cancer survivors at risk for osteoporosis due to cancer treatment. In large part, the most effective interventions have followed the ACSM exercise recommendations to preserve bone health in the general population [34]. ACSM recommends that women engage in weight-bearing endurance exercise (e.g., if walking, include intermittent jogging), appropriate impact activities (contraindicated for persons with known or suspected osteoporosis), and/or resistance exercise, or a combination thereof that produces moderate-to-high bone-loading forces for 3–5 days per week for endurance exercise and 2 to 3 days per week for resistance and/or impact exercise. Session durations should last 30–60 minutes.

For individuals with known or suspected osteoporosis, contraindicated movements include those that place an excessively high load on fragile skeletal sites. These include the following: high-impact loads, hyperflexion or hyperextension of the trunk, flexion or extension of the trunk with added resistance, and dynamic twisting motion. At this time, it may not be safe to prescribe bone-loading exercises for cancer survivors with bone fragility associated with osteoporosis or bony metastases in the hip or spine**.** Furthermore, it may not be appropriate to prescribe impact loading for individuals with joint/orthopedic issues and/or stability problems who may be better served by an exercise program aimed at reducing fall risk. Further research is needed to confirm whether or not the same osteogenic exercise programs that promote bone health in persons without cancer is effective and safe for cancer survivors.

Falls

There is increasing evidence that men and women fall more frequently after cancer treatment than before and compared to persons who have never had cancer [35, 36]; thus, for individuals for whom bone loading may be contraindicated due to age, orthopedic limitations, or balance disorders, a fall prevention program that focuses on lower body strength, balance, and mobility would be a reasonable strategy to lower fracture risk. Falls are associated with other injuries, including traumatic brain injury, and once a person has fallen, they can develop a fear of falling that leads to activity restrictions and more sedentary behavior. Trials to determine whether the same types of exercise that reduce age-related falls (e.g., strength training, tai chi training) are similarly effective at preventing falls associated with cancer treatment are underway [37].

There are no randomized controlled trials to date in cancer survivors with falls as a primary endpoint. There are several challenges to this type of research, including the relatively rare occurrence of falls and the large sample and time needed to observe a change in falls from an intervention. Similarly, the causes of falls associated with cancer treatment have not been fully characterized and may be due to more than an acceleration of the risks associated with age-related falls (i.e., muscle weakness and poor balance), but may also be due to treatment-related toxicities, such as hearing loss, ataxia, peripheral neuropathies, and fatigue, creating a challenge to develop new exercise-based approaches to fall prevention. In the absence of any evidence-based fall prevention studies in cancer survivors, it seems reasonable to consider standard fall prevention exercise approaches that reduce the risk of age-related falls for cancer survivors with a fall history to at least reduce the risk of falls that may be associated with advanced age [38, 39].

When prescribing exercise for survivors with fall history or problems with balance and lower extremity weakness, a multi-component program should seek to improve muscle strength, endurance, flexibility, range of motion, and balance. While this recommendation has not been extensively tested in large clinical trials, fall prevention research clearly demonstrates that these should be key components of an exercise program [40]. Functional exercises and core strengthening can improve balance, reduce risk of falls and fractures, and build movement confidence [40–42]. Clinicians and fitness professionals are advised to assess balance prior to recommending balance exercises so that the difficulty level can be adjusted according to baseline ability. There are several static and dynamic balance tests, such as the Single or tandem stance tests, Berg Balance Scale, BESTest, Fullerton Advanced Balance Scale, Physical Performance Test, Tinetti POMA, and Short Physical Performance Battery (SPPB). If a simple balance test is desired, the single-leg stance test with staff support to ensure that patient does not fall is a very brief and clinically practical measure with available normative data. If a more comprehensive test of function and balance is desired, the SPPB is a good

option. The protocol, scoring, and training materials, including videos, are available from the National Institute on Aging at: https://www.nia.nih.gov/research/labs/leps/short-physical-performance-battery-sppb.

Cardiac and Pulmonary Dysfunction

Cardiac complications of cancer treatment may emerge many years after treatment has ended for breast cancer, non-Hodgkin's and Hodgkin's lymphoma, testicular cancer survivors, and cancers treated with hematopoietic transplant [43, 44]. Morbidity from cardiovascular disease poses a significant burden for cancer survivors and translates into impaired quality of life and excess mortality [45]. Heart failure is a common acute side effect of some chemotherapy agents (e.g., trastuzumab and doxorubicin), and it may develop many years after treatment has ended [46]. Hypertension, arrhythmias, arterial stenosis, conduction disorders, and valvular disease are emerging as significant late effects of treatment [46, 47].

While these cardiac conditions are recognized as late effects of treatment, exercise intervention studies are being conducted to examine the effects of exercise on cardiac function in long-term survivors. Some studies have observed that breast cancer survivors have accelerated aging primarily related to severe declines in cardiac function that can be reversed with exercise [48, 49]. Other research suggests that structured exercise rehabilitation for testicular cancer survivors may prevent cardiovascular disease [50]. A growing body of evidence suggests that progressive aerobic exercise prescription may reverse and prevent some of the cardiopulmonary complications of cancer treatment [50]. Clearly, more research is needed in this emerging field to understand and determine the optimal dose, duration, and timing of structured exercise interventions to possibly prevent or minimize the declines in cardiac function.

Pulmonary dysfunction may emerge as a late effect of treatment. Compromised pulmonary function may impair daily function and may be caused by bleomycin, and mediastinal radiation [46]. Pulmonary dysfunction is manifest as pulmonary fibrosis, bronchiectasis, chronic pleural effusions, and recurrent pneumonia [46, 51, 52]. Decreased lung function can contribute to fatigue and lead to declines in functional ability. Some studies report a correlation between fatigue and cardiac and pulmonary dysfunction [53–56].

Exercise is an important and often-overlooked intervention for the promotion of cardiac and pulmonary health in long-term cancer survivors [57]. Prescribing exercise for survivors with a history of cardiac or pulmonary disease related to cancer requires specialized training and adherence to the well-established ACSM exercise testing and prescription guidelines [58–60]. While some survivors will benefit from clinically supervised exercise, others may be able to obtain medical clearance to participate in either clinically supervised exercise in a gym or participate a community-based exercise program. Either way, exercise prescription needs to account not only for the cardiopulmonary conditions of the survivor but any other cancer-related

side effects they may experience and other comorbid conditions they have. These patients are complicated and may require greater attention to daily variations in their condition and consequently, finer manipulation of an exercise prescription.

Overweight/Obesity

Weight control is an important issue in survivorship [45, 61–63]. Weight control is important to maintaining optimal health, preventing chronic diseases (e.g., type 2 diabetes mellitus, heart disease), and reducing the risk of recurrence and second cancers associated with being overweight [17, 61]. Overweight, obesity, and inactivity are associated with many different types of cancers, specifically breast, colorectal, endometrial, esophageal, renal, and pancreatic cancers [64]. The likelihood of developing bladder, liver, cervical, ovarian, and prostate cancer, as well as non-Hodgkin's lymphoma and multiple myeloma, is increased in people who are overweight or obese. Overweight and obesity are exceedingly common in healthy Americans, affecting two out of three people, and the incidence is higher among cancer survivors [65, 66]. Recommendations for weight control include seeking a balance between calories consumed and energy expended by increasing physical activity.

Recommending exercise for overweight and obese cancer survivors must focus on their baseline functional ability and, of course, the interplay of other cancer-related side effects and comorbid conditions. While no clear evidence-based exercise prescription is recommended specifically for overweight/obese cancer survivors, clearly assessing their functional ability and muscle strength is essential to developing a safe and effective exercise program that will increase caloric expenditure to promote weight loss and provoke positive changes in body composition.

Endocrine Dysfunction

Endocrine function can be disrupted by many cancer treatments causing growth hormone deficiency, hypothalamic leptin resistance, altered energy intake, energy storage, body fat distribution, and impaired satiety signaling [45, 67, 68]. Chemotherapy and radiation therapy can cause hypothyroidism, infertility, diabetes mellitus, and premature menopause [45]. Anti-estrogen therapy with drugs, such as Arimidex, Faslodex, or Tamoxifen, can be associated with vasomotor instability (hot flashes), arthralgias, and bone loss leading to osteopenia and osteoporosis [40, 45, 69]. Prostate cancer treatments to ablate testosterone commonly lead to muscle wasting and weakness, loss of bone density, vasomotor instability, gains in body fat and fatigue [45, 70, 71]. The newer immunotherapy drugs, such as sunitanib and checkpoint inhibitors, can cause profound endocrine dysfunction leading to diabetes, thyroid and pituitary dysfunction. While the interplay of physical activity

may not be known for all of these drugs, the evidence is clear that it can minimize effects of muscle weakness, improve body composition, and reduce fatigue. While research suggests that exercise may mitigate some of the effects of vasomotor instability, exercise will not prevent infertility or many of the endocrine dysfunctions that occur. However, a well-designed exercise prescription may help to prevent some of the side effects such as arthralgias, declines in bone density, and negative changes in body composition while also improving quality of life, confidence, and emotional outlook [40, 69–71].

Immune Dysfunction

Impaired immune function is being recognized as an emerging late effect of aggressive and often prolonged treatment after bone marrow transplant and B-cell lymphoma [72]. Radiation therapy and several chemotherapy drugs (e.g., rituximab) are associated with this late effect [46, 73, 74]. While no studies have explored the benefits of exercise for cancer survivors with immune deficiency, one can extrapolate from research in immunology to speculate that moderate exercise is beneficial to not only stimulate the immune system but also improve physical and emotional health of the survivor. However, there is a balance, as observed in elite athletes who over train and get sick; excessive exercise may further suppress immune function in a cancer survivor with immunodeficiency disorder. So, clearly, there is an equilibrium that must be considered when developing an exercise prescription for this group of survivors. As cancer survivors live longer, we are beginning to see immunodeficiency disorders as a late effect of survivorship and exercise studies to determine optimal exercise dose will be needed for this group of survivors.

Summary

Exercise prescription for cancer survivors necessitates a knowledge and understanding of cancer, the side effects of cancer treatment and the interplay of other comorbid conditions. This balance is key in developing individualized exercise prescriptions to optimize recovery and attainment of goals that are meaningful for the survivor. Gradual increases in exercise intensity and duration must be balanced with exercise tolerance and side effects to maximize the physical and psychological benefits. At every follow-up medical visit, all cancer survivors should be encouraged to exercise following the ACSM exercise guidelines for cancer survivors [12] and referred to appropriate clinical or community-based exercise programs. Inquiring about exercise tolerance and modifying and exercise prescription according to not only tolerance but also individual preferences is vital to successful exercise prescription.

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Chapter 14
Cardio-oncology

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A Dilemma in Cancer: Cardiovascular Risk

Direct toxicities of cancer treatments put patients at increased risk of cardiovascular disease (CVD), both in the acute phase of cancer treatment and throughout long-term survivorship [1–6]. For example, anthracyclines, one of the most commonly used antineoplastic drugs, are associated with dose-dependent changes in left ventricular (LV) function and development of chronic heart failure [7]. Radiation therapy, particularly that directed to the mediastinal area as experienced by breast and lung cancer as well as certain lymphoma patients, is associated with premature coronary artery disease (CAD) leading to long-term risk of cardiomyopathy and myocardial infarction (MI) as well as other types of heart disease (e.g., valvular disease, pericarditis) [5]. Monoclonal antibodies (e.g., trastuzumab) and tyrosine kinase inhibitors (e.g., lapatinib), directed at the extracellular proteins of tumor cells, have off-target effects on the heart that can result in changes in left ventricular function leading to a higher susceptibility to cardiac events both acutely and well after treatment has ended [8, 9]. Finally, as immunotherapy is emerging as a new tool in cancer treatment, its adverse acute cardiac effects are beginning to be elucidated and have been found to include vasculitis, autoimmune-mediated pericarditis, myocarditis, and acute-onset heart failure. Longer follow-up and monitoring are needed to determine long-term cardiac consequences of these novel cancer therapies [4, 10, 11].

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In addition to cancer treatment itself, an accelerated accumulation of CVD risk factors in cancer patients in combination with poor lifestyle behaviors contributes to long-term CVD risk in this population. This conceptual model of CVD risk in cancer patients has been coined the "multiple-hit" hypothesis [12]. Here, we provide an overview of the evidence regarding the burden of CVD risk factors and risk of overall CVD morbidity and mortality in cancer patients, organized by timing of diagnosis into childhood/adolescent and young adult (AYA) and adult cancers. We discuss the role of exercise to modify CVD risk factors, cardiorespiratory fitness, and CVD mortality in cancer patients. Lastly, we discuss strategies in the survivorship setting for childhood and AYAs to improve physical activity to optimize cardiovascular health and provide the rationale for exercise interventions in combination with CVD risk factor management in adult cancer patients leveraging a cardiac rehabilitation model to reduce overall CVD.

Cardiovascular Risk Factor Burden in Cancer

Childhood and AYA Cancers

Childhood and AYA cancer patients and survivors experience both direct and indirect cardiac insults that increase the prevalence of CVD risk factors relative to similarly aged individuals without a cancer diagnosis. For example, adult survivors of childhood cancer are more likely than sibling controls to need medications for hypertension (odds ratio [OR], 1.9; 95% CI, 1.6–2.2), dyslipidemia (OR, 1.6; 95% CI, 1.3–2.0), or diabetes (OR, 1.7; 95% CI, 1.2–2.3) [13]. These findings were similar to those of a German cohort of childhood cancer survivors, in which Faber et al. found an increased risk of hypertension (relative risk [RR], 1.4; 95% CI, 1.2–1.6) and dyslipidemia (RR, 1.3; 95% CI, 1.1–1.4) in survivors compared to the general population, which represented a premature occurrence of 6 and 8 years, respectively, for these diagnoses [14]. Childhood cancer survivors have also been shown to have a high prevalence of metabolic syndrome, with Smith et al. reporting that 31.8% of 1598 survivors studied met the criteria for metabolic syndrome at a mean of 25.6 years post-diagnosis [15]. Oeffinger et al. reported significantly higher measurements of insulin resistance among survivors of childhood ALL compared with healthy controls [16]. Similarly, Ozdemir et al. found that survivors of childhood ALL had a prevalence of 14%, 38%, 42%, and 5% for insulin resistance, dyslipidemia, overweight/obesity, and metabolic syndrome, respectively, at a median of 4.5 years post-diagnosis [17]. In AYA survivors, Tai et al. assessed health behaviors and CVD risk factors utilizing data from the 2009 Behavioral Risk Factor Surveillance System. Compared with respondents without a history of cancer, a greater percentage of AYA survivors did not perform any physical activity in the past month (30.8% [95% CI: 27.2–34.7%] vs. 26.7% [95% CI: 26.4–27%]) and a greater percentage had diagnosed hypertension (35.1% [95% CI: 31.6–38.7%] vs. 29.1% [95% CI: 28.9–29.4%]) and diabetes (11.8% [95% CI: 10–14%] vs. 9.0% [95% CI: 8.9–9.2%]) [18].

Body composition changes and loss of physical activity can occur during and after treatment for childhood cancer and ultimately contribute to the premature development of CVD risk factors in this population. In a systematic review and meta-analysis, Wang et al. reported that survivors of childhood brain cancers had similar rates of overweight/obesity compared with general population controls; however, survivors had higher percent fat mass (mean difference, 4.1%; 95% CI, 2.0–6.0) than controls [19]. In the Childhood Cancer Survivorship Study (CCSS), survivors of leukemia were more likely to be obese compared with general population controls (females: OR, 1.5; 95% CI, 1.2–1.8; males: OR, 1.2; 95% CI, 1.0–1.5) [20]. In the same cohort, body mass index (BMI) of survivors was assessed longitudinally, with ALL survivors who were treated with cranial radiation exhibiting a significant increase in BMI over time compared with sibling controls [21]. Additionally in the CCSS, childhood cancer survivors have been found to be more likely to be physically inactive, defined as not meeting the Centers for Disease Control and Prevention (CDC) guideline of 150 min of moderate or 60 min of vigorous intensity physical activity each week, compared with sibling controls (OR. 1.2; 95% CI, 1.1–1.3) [22]. In a separate study within the CCSS, of 9301 survivors of childhood cancers, 46% were found to meet CDC activity guidelines, compared with 52% of sibling controls ($P < 0.001$), with survivors of medulloblastoma and osteosarcoma reporting the highest level of physical inactivity [23].

Adult Cancers

Similar to findings in childhood cancer, it has been shown that survivors of adult cancer are more likely to be diagnosed with diabetes (14% vs. 9%, $P < 0.001$), dyslipidemia (50% vs. 44%, $P < 0.001$), and hypertension (60% vs. 49%, $P < 0.001$), compared with the general population [24]. Keats et al. compared CVD risk factors among 1526 survivors of adult cancers with age- and sex-matched non-cancer controls, finding that cancer survivors were more likely to report a history of hypertension (OR, 1.6; 95% CI, 1.0–1.3) and/or diabetes (OR, 1.3; 95% CI, 1.0–1.2) and less likely than controls to engage in high levels of physical activity (OR, 0.8; 95% CI, 0.7–0.9) [25]. Weaver et al. also compared CVD risk factors in cancer survivors with the general adult population, reporting that 62% of survivors were overweight or obese, 55% had hypertension, 21% had diabetes, and 18% were inactive, with all of these CVD risk factors significantly more common among survivors compared with controls [26]. Finally, in a meta-analysis of nine cross-sectional studies assessing risk of metabolic syndrome among cancer survivors, Jung et al. determined that, compared with healthy control groups, survivors were at increased risk of metabolic syndrome (OR, 1.8; 95% CI, 1.1–3.0) [27].

Weight gain and physical inactivity during and after cancer treatment also contribute to CVD risk factor burden in adult patients. For example, Courneya et al. assessed physical activity and obesity in survivors of adult cancers, utilizing the Canadian Community Health Survey to assess more than 1 million cancer survivors, and found that less than 22% were physically active (defined as the equivalent of

walking ≥30 min/day) and 18% were obese [28]. Among 1282 long-term breast cancer survivors who underwent adjuvant endocrine therapy, Raghavendra et al. found that 34% had a weight gain of >5% body mass after 5 years of therapy [29]. Gross et al. assessed weight change over time in breast cancer survivors and cancer-free controls, finding that survivors gained significantly more weight over 4 years of follow-up (mean difference, 3.1 pounds; 95% CI, 0.9–5.2) compared to controls [30]. In terms of physical activity, Boyle et al. collected 7 days of accelerometer data among breast cancer survivors ($n = 259$, mean 3 years post-diagnosis), finding that only 16% of survivors met physical activity guidelines [31]. In addition, Hair et al. assessed pre- and post-diagnosis physical activity among 1735 breast cancer survivors, reporting that, in the post-diagnosis period, 35% of survivors met physical activity guidelines, and that 59% of survivors decreased their physical activity from pre- to post-diagnosis, with an average decrease of 15 metabolic equivalent task (MET) hours (95% CI: 12–19 MET hours) [32]. Similar reports of weight gain and changes in physical activity have been demonstrated in several different cancer types, including ovarian, colorectal, and prostate cancers [33–36].

Taken together, there is robust data that childhood/AYA and adult cancer survivors have a higher burden of CVD risk factors, such as hypertension, dyslipidemia, and metabolic syndrome, compared to the general population. These factors, in combination with prior cancer exposures and physical inactivity and weight gain, likely play a pivotal role in the increased risk of cardiovascular morbidity and mortality seen in cancer survivors as discussed below.

Cardiovascular Morbidity and Mortality in Cancer

Childhood and AYA Cancers

The premature development of a variety of cardiac diagnoses including coronary disease, heart failure, and valvular disease is of major concern in the childhood and AYA cancer population [37]. For example, in the CCSS, Mulrooney et al. evaluated the risk of CVD in 14,358 childhood cancer survivors compared to sibling controls, finding that survivors were significantly more likely to report congestive heart failure (HR, 5.9; 95% CI, 3.4–9.6), pericardial disease (HR, 6.3; 95% CI, 3.3–12.0), myocardial infarction (HR, 5.0; 95% CI, 2.3–10.4), or valvular abnormalities (HR, 4.8; 95% CI, 3.0–7.6) at a median of 21 years post-diagnosis [38]. In a cohort including 32,308 childhood cancer survivors in Scandinavia, Gudmundsdottir et al. reported that, compared to population controls, survivors had a twofold higher risk of any CVD diagnosis (RR, 2.1; 95% CI, 2.0–2.2), with the highest risks for heart failure (RR, 5.2; 95% CI, 4.5–5.9), valvular dysfunction (RR, 4.6; 95% CI, 3.8–5.5), and cerebrovascular diseases (RR, 3.7; 95% CI, 3.4–4.1) [39]. Similarly, in 5673 survivors of AYA cancer, Chao et al. found a greater than twofold increased risk of CVD compared to healthy controls (adjusted incidence rate ratio, 2.4; 95% CI, 1.9–2.9) at a mean follow-up of 4.4 years, with survivors of leukemia and breast

cancer at highest risk (adjusted incidence rate ratio, 4.2, 95% CI, 1.7–10.3 and 3.6, 95% CI, 2.4–5.5, respectively) [40]. In a Danish cohort of 43,153 survivors of AYA cancers, it was reported that survivors had a higher risk of cardiac hospitalizations than would be expected in the general population (RR, 1.30; 95% CI, 1.28–1.33), with survivors of Hodgkin lymphoma at high risk for hospitalization with valvular disease and survivors of leukemia at high risk for cerebral hemorrhage and cardiomyopathy hospitalizations [41].

Cardiac death has also been found to be elevated among survivors of childhood and AYA cancers. In the CCSS, Armstrong et al. reported that childhood cancer survivors at 30 years post-diagnosis were 7 times more likely than the general population to die of cardiac causes (standardized mortality ratio [SMR], 7.0; 95% CI, 5.9–8.2] [42]. Similarly, among 34,489 survivors of childhood cancer with a mean follow-up of 18 years, Fidler et al. found an increased risk of cardiac mortality of 3.4 times expected, with survivors at 2.5 and 5.9 times greater risk of ischemic heart disease and cardiomyopathy/heart failure death, respectively, than expected compared to the general population [43]. In a systematic review and meta-analysis of studies that assessed cardiac mortality in long-term lymphoma survivors, Boyne et al. reported that the pooled number of deaths attributed to CVD among Hodgkin and non-Hodgkin lymphoma was estimated to be 7.3 (95% CI: 5.3–10.1) and 5.4 (95% CI: 2.6–11.2) times that expected in the general population [44]. Lastly, in survivors of AYA cancer, the likelihood of cardiac death is higher, compared with the general population, with a reported standardized mortality ratio (SMR) at a mean follow-up of 19.3 years post-diagnosis of 1.4 (95% CI: 1.3–1.4). When stratified by age at diagnosis, those diagnosed earlier in life (ages 15–19 years) had the highest risk of cardiac mortality (SMR, 4.2; 95% CI, 3.4–5.2), and when stratified by type of cancer, the highest risk was found among survivors of Hodgkin lymphoma (SMR, 3.8; 95% CI, 3.5–4.2) [45].

Adult Cancers

Similar to childhood and AYA survivors, risk of developing CVD is elevated in adult cancer survivors relative to the general population. Armenian et al. studied 36,232 survivors of adult onset cancers with 73,545 matched (age, sex, and residential ZIP code) non-cancer controls, finding that survivors of multiple myeloma (incidence rate ratio [IRR], 1.7; 95% CI, 1.3–2.2), lung/bronchus cancer (IRR, 1.58; 95% CI, 1.3–1.9), non-Hodgkin lymphoma (IRR, 1.4; 95% CI, 1.2–1.7), and breast cancer (IRR, 1.1; 95% CI, 1.1–1.2) had a significantly higher risk of developing ischemic heart disease, stroke, and cardiomyopathy/heart failure [46]. Among 1379 survivors of hematopoietic cell transplantation, at a median follow-up time of 7 years, Chow et al. reported that the 10-year cumulative incidence of ischemic heart disease, cardiomyopathy, stroke, and all-cause cardiovascular death was 3.8%, 6.0%, 3.5%, and 3.7%, respectively [47]. In 10-year survivors of breast cancer, Hooning et al. found increased risks of congestive heart failure (HR, 2.7; 95% CI, 1.3–5.6) and valvular dysfunction (HR, 3.2; 95% CI, 1.9–5.3) among those treated

with radiotherapy, compared with the general population [48]. In addition, among 26,213 survivors of adult cancers, Khan et al. determined that, compared with age- and sex-matched controls, breast cancer survivors at a mean of 10.2 years post-diagnosis had increased risk of heart failure (HR, 2.0; 95% CI, 1.3–3.0) and coronary artery disease (HR, 1.3; 95%, CI 1.1–1.4) [49].

Mortality from CVD in adult cancer survivors is most studied in breast and gynecologic cancers. Bradshaw et al. compared CVD mortality among 1413 breast cancer survivors and 1411 age-matched controls without a breast cancer history, finding that survivors had a higher risk of CVD mortality (HR, 1.8; 95% CI, 1.5–2.1) [50]. The Surveillance, Epidemiology, and End Results (SEER) registry has been used to determine mortality data among cancer survivors in multiple studies. For example, among 67,514 survivors of ductal carcinoma in situ (DCIS), Berkman et al. reported a 20-year cumulative incidence of 13.2 (95% CI: 12.8–13.7) for CVD death, compared with a cumulative incidence of 3.2 (95% CI: 3.0–3.4) for breast cancer death [51]. Also using SEER, Dinkelspiel et al. assessed mortality in 67,385 ovarian cancer survivors, finding that, over a median follow-up of 6.5 years, 4.2% (95% CI: 3.8–4.5%) of those with stage I neoplasms died due to CVD and for those with stage III–IV tumors, 2.3% (95% CI: 2.2%–2.4%) died due to CVD [52]. Finally, in two separate SEER analyses of death among endometrial cancer survivors, Felix et al. reported that survivors were more likely than the general population to die of CVD (age-adjusted SMR, 8.8; 95% CI, 8.7–9.0) [53], and Ward et al. reported that CVD mortality was the most common cause of death in this population (35.8%; 95% CI, 35.3–36.3%) [54].

In prostate cancer, the observational and clinical trials data on CVD risk are discordant. In a meta-analysis of observational data, Bosco et al. determined that, compared to prostate cancer patients not receiving androgen deprivation therapy (ADT), treatment with ADT was associated with a higher risk of fatal or nonfatal myocardial infarction (HR, 1.6; 95% CI, 1.3–1.9) [55]. In contrast, Nguyen et al. demonstrated no excess cardiovascular death in prostate cancer patients receiving ADT vs. no ADT (HR, 0.9; 95% CI, 0.8–1.1) based on a meta-analysis of eight randomized clinical trials [56]. Selection bias among patients offered ADT and differences in study design and populations included may explain discrepancies in prior studies, though there is general agreement that older men receiving ADT and those with a prior cardiac history are at higher risk for recurrent CVD events [57, 58].

In summary, excess CVD morbidity and mortality is striking in the childhood and AYA population and in the adult breast cancer population, with data emerging for other site-specific cancers.

The Importance of Exercise in Cancer Care from the Cardiologist Perspective

In the general population, exercise is a known strategy to reduce body weight, optimize blood pressure, and reduce risk of incident diabetes and metabolic syndrome [59–61]. In addition, exercise increases cardiorespiratory fitness (CRF) or VO_{2peak}, a

key predictor of survival [62–65]. Herein, we provide the current evidence regarding the impact of exercise on CVD risk factors, CRF, and CVD mortality in the childhood/AYA and adult cancer populations.

Exercise and CVD Risk Factors in Cancer

Childhood and AYA Cancers

Studies that have assessed the impact of exercise training on CVD risk factors among survivors of childhood and AYA cancers are sparse. Jarvela et al. performed a 16-week home-based exercise intervention in 17 survivors of childhood ALL. The intervention included instructions for undertaking a resistance training routine 3–4 times/week as well as aerobic exercise of participants' choice for 30 min 3 times/week with participants receiving a pedometer and daily step goals. At the end of the intervention, compared to pre-intervention results, survivors had improvements in fasting plasma insulin (10.1–7.0 mU/L, $P = 0.01$), homeostatic model assessment-insulin resistance (HOMA-IR) (2.2–1.5, $P = 0.002$), waist circumference (84–82 cm, $P = 0.003$), and body fat percent (27.7–26.8%, $P = 0.04$) [66]. Assessing adult survivors of childhood cancer who underwent hematopoietic cell transplantation, Slater et al. found that those survivors who had higher exercise capacity (assessed via 6-min walk test) had lower waist circumference (77.8 ± 2.6 vs. 87.8 ± 2.5 cm, $P < 0.001$), percent fat mass (33.6 ± 1.8 vs. 39.4 ± 1.7%, $P < 0.001$), and higher insulin sensitivity (10.9 ± 1.0 vs. 7.42 ± 1.14 mg/kg/min, $P = 0.01$) compared to those survivors with lower exercise capacity [67]. In a similar study by Slater et al., the group assessed physical activity level and CVD risk factors among 319 childhood cancer survivors, finding that the high physical activity group (those who performed >60 min/day) had lower percent fat mass (24.4 ± 1.3% vs. 29.8 ± 0.9%, $P < 0.001$), abdominal visceral fat (20.0 ± 1.8 vs. 24.9 ± 1.3 cm^3, $P = 0.007$), and greater lean body mass (41.3 ± 0.7 vs. 39.5 ± 0.5 kg, $P = 0.009$) than the low physical activity group [68].

Adult Cancers

The effects of exercise on body weight and CVD risk factors, such as metabolic syndrome, have been best described in the breast cancer population. For example, in overweight breast cancer survivors, Swisher et al. randomized participants to either a control group or an intervention group that included 3 supervised and 2 unsupervised exercise sessions per week for 12 weeks, with a goal of completing 150 min/week of moderate intensity exercise as defined by 60–75% of peak heart rate achieved on the exercise test. At the end of 12 weeks, intervention participants lost more body fat than control participants (2.4% loss vs. 0.4% gain, $P < 0.05$) [69]. Similarly, assessing the effect of exercise on body fat percentage in inactive breast

cancer survivors, Irwin et al. performed a randomized controlled trial with the intervention group participating in 150 min/week of supervised gym and home-based moderate-intensity aerobic exercise. At the end of 12 weeks, body fat percent in the intervention group decreased, compared to an increase seen in the control group (−1.9% vs. +1.1%, $P = 0.002$) [70]. In a 12-week intervention among 20 patients undergoing chemotherapy for breast cancer, Kim et al. had participants exercise 5 days/week in a supervised setting with target HR goals of 40–60% peak for a total of 30–40 min of walking. At the end of the intervention, compared to pre-intervention measurements, BMI had decreased by 1.6% ($P = 0.002$) and percent fat mass decreased by 3.1% ($P = 0.05$) [71].

Dieli-Conwright et al. performed a 16-week randomized controlled trial of a combined aerobic and resistance exercise intervention among overweight and obese breast cancer survivors, finding that, compared with the control group, the intervention improved all components of the metabolic syndrome (e.g., blood pressure, cholesterol) ($P \leq 0.001$ for all), measures of sarcopenic obesity ($P = 0.001$ for all), and circulating biomarkers including insulin ($P = 0.002$) and adiponectin ($P = 0.001$) at 3-month follow-up [72]. Looking at similar outcomes, Thomas et al. performed a randomized controlled trial among 65 breast cancer survivors with the exercise group performing 3 supervised and 2 unsupervised exercise sessions per week with a goal of completing 150 min/week of moderate aerobic activity (60–80% maximal predicted heart rate). After 6 months, those who adhered to the intervention group had significantly lower metabolic syndrome z-scores compared to those who did not adhere (−0.76 vs. +0.80, $P = 0.009$) [73]. Ligibel et al. instructed sedentary overweight breast cancer survivors to perform 90 min/week of home-based aerobic activity in addition to 2 supervised resistance training sessions per week for a total of 16 weeks, finding that survivors in the exercise group had a decrease in fasting insulin concentration from pre- to post-intervention (mean decrease of 2.9 microU/mL, $P = 0.03$), with no significant change seen in the control group [74]. In another study, Irwin et al. randomized 75 postmenopausal breast cancer survivors to either a control or exercise group with the exercise group completing 3 weekly supervised and 2 weekly home-based sessions each week including 15–30 min of aerobic activity. At the end of 6 months, the exercise group had a 1.8 μU/mL (7.1%) reduction in insulin levels, and the control group had an increase in insulin levels by 3.5 μU/mL (13.6%), which corresponded to a 20.7% between-group difference ($P = 0.09$) [75]. Finally, in a meta-analysis of 18 studies of exercise interventions performed among breast cancer survivors, Kang et al. reported that exercise significantly reduced fasting insulin levels in this population (weighted mean difference, −3.5 μU/mL; 95% CI, −6.0 to −1.0) [76].

While less abundant, there is data on successful exercise interventions for other site-specific cancers. For example, in a 6-month intervention, Brown et al. randomized 39 colon cancer survivors to usual care, low-dose aerobic exercise (150 min/week), or high-dose aerobic exercise (300 min/week) at moderate intensity, finding that exercise was associated with a significant reduction in waist circumference in the high-dose (−4.52 cm ± 1.34) group and in the low-dose group (−1.46 cm ± 1.29) compared to the usual care group [77]. In addition, insulin resistance, as

measured by HOMA, showed exercise dose-dependent improvements (−0.43 ± 0.19 in the high-dose group, −0.63 ± 0.17 in the low-dose group, and −0.11 ± 0.20 in the control group, nonlinear $P_{trend} = 0.01$) [78]. In a trial among men undergoing ADT for prostate cancer ($n = 32$), Focht et al. randomized patients to a 12-week exercise intervention consisting of 2 weekly sessions (30 min aerobic + 30 min resistance training) that were supervised for weeks 1–6 and performed independently during weeks 7–12. Compared to the control group, significant improvements in the exercise group were seen from baseline to 12-week follow-up in body fat percentage ($P < 0.05$) and body fat mass ($P < 0.03$) [79].

In summary, exercise training is a demonstrated strategy in adult cancer survivors (predominately breast) to lose body weight, improve measures of body composition and insulin resistance, and to alter key CVD risk factors such as blood pressure and cholesterol. In the childhood and AYA cancer populations, the majority of exercise trials that have been performed focus on functional outcomes, such as hand grip strength, and patient-reported outcomes, such as quality of life. More studies are needed in this population to assess the impact of exercise on measurable CVD risk factor outcomes.

Exercise, Cardiorespiratory Fitness and CVD in Cancer

Childhood and AYA Cancers

The effects of exercise on CRF and CVD outcomes are limited in the childhood/AYA population. Jarvela et al. studied 17 AYA survivors of childhood ALL who participated in a home-based exercise program that included at least 3 days/week of 30-min aerobic exercise sessions and 3–4 sessions/week of resistance training. At 16 weeks, CRF significantly improved from 35.2 to 37.1 ml kg^{-1} min^{-1}($P = 0.01$) [66]. In a second study, Braam et al. assessed the impact of reported physical activity on CRF among 60 children with cancer, finding that each additional minute of physical activity resulted in an increase in VO_{2max} of 0.05 ml kg^{-1} min^{-1}, while each additional minute of sedentary behavior reduced VO_{2max} of 0.06 ml kg^{-1} min^{-1} [80]. In the only study on CVD outcomes in this population, Jones et al. assessed exercise behavior via questionnaire among 1187 survivors of childhood Hodgkin lymphoma, finding that cumulative incidence of any cardiovascular event at 10 years of follow-up was 5% for survivors reporting the calculated equivalent of ≥9 MET h/week compared to 12% for survivors reporting no exercise ($P < 0.001$) [81].

Adult Cancers

There is a growing body of literature regarding the impact of exercise training on CRF among adult cancer patients. A systematic review of 18 exercise training trials including cancer patients in the pre-surgical setting found that exercise training

prior to surgery was associated with an overall improvement in CRF of 8–32% [82]. The effects of exercise training during cancer treatment, however, appear more modest. In systematic review and meta-analysis of studies assessing exercise training during active breast cancer, Schmitz et al. found only weak evidence to show that exercise interventions improve CRF in this population [83]. While exercise during active cancer treatment may not improve CRF, evidence does show that exercise mitigates the loss of CRF that typically occurs during active treatment. For example, a trial involving breast cancer patients found that participation in a progressive aerobic exercise training regimen 3 times per week at 70% of Vo_{2max} resulted in no change in CRF (0.2 ml kg^{-1} min^{-1}), whereas the control group experienced a significant loss in CRF (−1.6 ml kg^{-1} min^{-1}) [84]. A secondary analysis of the data gathered during this study showed that a longer duration of aerobic exercise training (50–60 min per bout rather than 25–30 min per bout) at a constant intensity (70% PHR) and frequency (3 times per week) was most successful at mitigating CRF loss among breast cancer patients undergoing adjuvant chemotherapy compared to other exercise regimens [85].

Exercise has the greatest impact on CRF in the cancer population when performed in the survivorship setting. A meta-analysis of randomized controlled trials demonstrated a pooled increase in Vo_{2max} of 2.2 ml kg^{-1} min^{-1} ($P < 0.01$) among survivors of breast cancer, colorectal cancer, prostate cancer, lung cancer, and lymphoma [86]. For example, postmenopausal breast cancer patients participating in aerobic exercise training 3 times per week for 30 min each session at 70–75% of Vo_{2max} exhibited better CRF after 15 weeks than did patients receiving standard care ($P < 0.01$) [87]. Additionally, in a recent systematic review and meta-analysis of 48 randomized controlled trials in patients with adult-onset cancer ($n = 3632$) to evaluate the effects of exercise training on CRF, Scott et al. demonstrated that exercise training was associated with a significant increase in VO_{2max} (+2.80 ml kg^{-1} min^{-1}) compared with no change (+0.02 ml kg^{-1} min^{-1}) in the control group ($P < 0.001$) [88].

Exercise and CVD mortality outcomes are currently limited to self-reported data and predominately in breast cancer patients. Jones et al. assessed exercise behavior by questionnaire among 2937 women diagnosed with non-metastatic breast cancer finding that, at a median follow-up time of 8.6 years, increased exercise was associated with a decreased risk of cardiovascular events, including coronary artery disease, heart failure, valve abnormality, arrhythmia, stroke, or CVD death. Compared to women who exercised for the calculated equivalent of <2 MET h/week, the adjusted HR was 0.9 (95% CI: 0.8–1.1) for 2–10.9 MET h/week, 0.8 (95% CI: 0.7–1.0) for 11–24.5 MET h/week, and 0.7 (95% CI: 0.5–0.8) for ≥24.5 MET h/week [89]. Palomo et al. assessed questionnaire physical activity data and cardiac events among 4015 breast cancer survivors over a median follow-up time of 12.7 years, finding that those who participated in ≥9 MET h/week had lower risks of cardiovascular events (HR, 0.8; 95% CI, 0.6–1.0) and coronary heart disease death (HR, 0.6; 95% CI, 0.4–0.9), compared to those who participated in <9 MET h/week [90]. The only other reported data comes from the 1999–2009 National Health Interview Survey Linked Mortality Files that included 13,997 cancer patients. Tarasenko et al. showed that, compared with survivors who did not meet

aerobic exercise guidelines, those who met the guidelines had a reduced risk of CVD mortality (HR, 0.65; 95% CI, 0.6–0.8) [91].

Further studies are required to demonstrate the effects of exercise training on CRF as well as the long-term cardiovascular outcomes in childhood and AYA cancer survivors. Given the burden of CVD in this population, there is urgent need for research in this area. In regard to adult cancers, data is emerging that exercise training has clear benefit on CRF in cancer patients. Given that CVD risk burden extends beyond breast cancer, more exercise training studies on CVD outcomes are needed, particularly in gynecological, colorectal, and prostate cancer.

Beyond Clinical Trials and into Clinical Practice: Delivering Exercise to Cancer Patients and Survivors

Childhood and AYA Cancers

Given the known data that CVD morbidity and mortality is a serious competing risk in childhood and AYA cancer patients and survivors, strategies to mitigate CVD risk factor burden are needed, and we believe that exercise is an important component of these strategies. One of the earliest first published trials of exercise for childhood cancer survivors was published in 1993 by Sharkey et al. and utilized a 12-week pediatric cardiac rehabilitation model for 10 childhood cancer survivors. Survivors participated in twice-weekly, hour-long, supervised aerobic exercise sessions and added home-based exercise for the same duration and intensity (70–80% maximal heart rate) for a third weekly session during weeks 7–12. At the end of the intervention, exercise time increased an average of 13% during CPET ($P < 0.05$), with a trend toward improvements in Vo_{2peak} (mean increase 8%, $P = 0.1$) [92]. Since this time, many traditional supervised exercise interventions have been performed in the childhood and AYA cancer populations, but it has become increasingly recognized that this age group has different attitudes and psychology around exercise, compared to adults, and unique interventions may be more effective in promoting increases in physical activity [93]. Furthermore, this group has the potential for a long lifespan; thus, interventions that result in long-term health behavior changes (i.e., increased physical activity) are exceedingly important. Both adventure- and technology-based interventions have proven effective in this population. For example, Li et al. randomized 222 childhood cancer survivors aged 9–16 to either an adventure-based training program or a placebo intervention. The adventure-based program included 4 days of camping and outdoor games and ropes course activities, as well as health education sessions, while the placebo group attended a 4-day indoor activity session that included film viewing, board games, crafts, and health education sessions. Twelve months after the intervention, the adventure group performed significantly higher levels of physical activity, compared to the control group [94]. Valle et al. utilized Facebook to increase physical activity in young adult cancer survivors, with intervention participants gaining access to a Facebook group

with exercise-promoting strategies and messaging, group support, and goal setting. At the end of the 12-week intervention, the intervention group increased moderate to vigorous activity by 67 min/week compared to baseline ($P = 0.009$) [95]. However, despite demonstrated feasibility, not all technology-based interventions have proven effective in increasing physical activity in this population [96, 97]. This points to the need to continue to develop and trial unique interventions that appeal to the childhood/AYA survivorship population. While technology and social media is a major component, being physically active is also dependent on social interactions and time with friends; thus, targeting team- or community-based sports groups in this population may be another potential avenue.

Adult Cancers

While not yet available for cancer patients, a framework for exercise and CVD risk factor management in adults already exists in the form of cardiac rehabilitation (CR). CR is a multifaceted, multidisciplinary secondary prevention effort involving exercise training and physical activity counseling, nutrition counseling, risk factor management (e.g., hypertension, dyslipidemia, smoking, weight, diabetes), and psychosocial support in patients with a qualifying cardiovascular diagnosis [98]. As such, CR may be one potential solution from a cardiologist's perspective to engage cancer patients and survivors in exercise and CV risk modification. CR for cancer patients has already been tested as a vehicle for exercise training. For example, Dittus et al. utilized existing CR programming and staff for cancer survivors to participate in group supervised sessions (2 times/week aerobic exercise at 70–85% peak heart rate progressing from 20 to 40 min/session + resistance exercises). Adherence to the programming was 74%, and after 12 weeks, survivors had significant increases in 6-min walk distance (8.3% increase, $P = 0.03$) and muscular strength testing (21.5% increase, $P < 0.001$) [99]. Dolan et al. had early-stage breast cancer survivors exercise in the supervised CR setting once a week for 22 weeks in addition to home-based brisk walking 4 times/week at 60–80% peak heart rate. Resistance training and group educational seminars were also a component of the programming. At the end of 22 weeks, compared to baseline, participants VO_{2max} increased by 14% (21 ± 6 to 24 ± 7 ml kg^{-1} min^{-1}, $P < 0.001$) [100]. Lastly, Hseih et al. created an oncology rehabilitation program based on CR and assessed its impact on 96 breast cancer survivors. Survivors exercised in a supervised, group setting 2–3 times/week performing 40 min of aerobic exercise at 40–70% peak heart rate as well as 20 min of resistance exercise for 6 months. At the end of the intervention, VO_{2max} increased significantly, compared with baseline measurements (15–23% increase based on cancer treatment regimen, $P < 0.05$) [101].

These data are promising regarding the feasibility of CR in adult cancer patients to deliver exercise training and improve CRF. Importantly, CR is multimodal and is structured to provide bundled services. CR has the potential to provide an umbrella of additional services to adult cancer patients (including adult survivors of childhood

and AYA cancers) such as exercise and nutritional counseling, supervised exercise training, as well as surveillance of CVD risk factors and psychosocial stresses that contribute to CVD. Presently, CR is not available to cancer patients given a number of factors, most importantly, the fact that cancer is not a qualifying diagnosis for CR reimbursement by third-party payers. However, with the development of American College of Sports Medicine (ACSM) cancer certification for exercise trainers to broaden expertise in cancer-specific exercise, improved collaborations between oncologists and cardiologists, the development of upcoming guidelines to delineate cancer patient eligibility and timing for CR, and the potential research opportunities to test multimodal CR in cancer patients, the future of CR in cancer is promising.

Future Research and Directions

The future is now regarding the need to intervene to reduce the CVD morbidity and mortality of childhood/AYAs and adult cancer patients. Based on the evidence in this chapter, physical inactivity and weight gain are contributing causes to the burden of CVD risk factors found in cancer patients relative to the general population. While there is emerging data that exercise training can improve CVD risk factors and reduce CVD death in childhood cancer and AYAs, the data is still in its infancy. The science in adult cancers, particularly breast cancer, is compelling in regard to exercise as a strategy to improve CVD risk factors and CRF and is emerging for overall CVD. However, still lacking is a comprehensive model for both childhood/AYA and adult cancers to systematically engage and deliver exercise to cancer patients. Further work is also needed to characterize the mechanisms of potential CVD benefit as well as delineate the exercise training regimen or "dose" most protective from a cardiovascular standpoint across site-specific cancers.

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Chapter 15
Energetics

Leah M. Ferrucci and Melinda L. Irwin

Introduction

In the last two decades, considerable progress has been made in combating cancer. Significant advances in cancer detection and treatment, and changes in modifiable behaviors (primarily smoking cessation) have led to a 27% decline in cancer mortality rates from a peak in the mid-1990s [1, 2]. Because of this improved survival rate, as well as a growing older population, the number of cancer survivors in the United States and worldwide has increased substantially. Estimates from 2019 indicate nearly 16.9 million people (approximately 5% of the US population) are cancer survivors, an increase from 1.8% of the US population in 1978 [3]. This number is projected to grow to 21.7 million by 2029 [3].

As the number of cancer survivors has increased, the importance of understanding the needs of this population has also grown. Evidence continues to accumulate suggesting obesity plays a key role in both the risk of developing and dying of cancer. Obesity is the excessive accumulation of body fat. Body mass index (BMI, weight in kilograms divided by the square of height in meters) is a common proxy for assessing overall body fatness. Among adults, overweight is defined as a BMI of 25.0–29.9 and obesity as a BMI of 30 or more. Obesity can further be divided into class 1 (BMI, 30.0–34.9), class 2 (BMI, 35.0–39.9), and class 3 (BMI, ≥40.0). Interestingly, as cancer mortality rates have declined over the last two decades, the prevalence of obesity in the United States and globally has increased significantly over the last two decades. At present, more than one-third of the US adults are categorized as obese and two-thirds are categorized as overweight [4]. Data from the National Health Interview Survey indicate the prevalence of obesity in adults with a history of cancer increased from 22.4% to 31.7% between 1997 and 2014 and the rate of increase in cancer survivors was greater than in the general population [5].

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Based on a recent review of the epidemiologic literature, obesity was identified as a risk factor for 13 cancer types [6]. Incidence rates of several obesity-related cancer types have increased in the United States, in part, due to the increase in obesity prevalence [1]. Approximately 8% of all cancers (excluding nonmelanoma skin cancers) among adults are attributable to obesity [7, 8]. Obesity is primarily caused by poor diet and physical inactivity, which are also independent risk factors for cancer development and mortality. Taken together, obesity, diet, and physical activity are known as "energy balance" or "energetics." At present, research is still being conducted to understand the relationships between energy balance and carcinogenesis and survival.

This chapter discusses the observational findings related to energetics, with a focus on obesity and cancer risk and mortality; the mechanisms mediating this relationship; and effects of weight loss interventions utilizing exercise and/or diet interventions on numerous cancer outcomes. Outcomes addressed include cancer risk and mortality as well as biological, psychosocial, and behavioral outcomes associated with cancer. Our discussion of the intervention research is primarily of studies among adults diagnosed with cancer.

Observational Studies of Obesity and Cancer Risk and Mortality

Obesity and Cancer Risk

Recently, the International Agency for Research on Cancer (IARC) reported that there is sufficient evidence to conclude that avoidance of excess body fat is associated with a lower risk for cancers of the endometrium, esophagus (adenocarcinoma), gastric cardia, kidney (renal cell), multiple myeloma, meningioma, liver, pancreas, colorectum, gallbladder, breast (postmenopausal), ovary, and thyroid [6]. Associations from meta-analyses or pooled analyses ranged from 1.2 to 1.5 for overweight and 1.5 to 1.8 for obesity for cancers of the colon, gastric cardia, liver, gallbladder, pancreas, and kidney. The association for esophageal adenocarcinoma was quite strong, with a relative risk of 4.8 for a BMI of 40 or more. For each of these cancers, there was evidence for a dose–response relationship. IARC also concluded that there was limited evidence for an association between excess body fatness and fatal prostate cancer, diffuse large B-cell lymphoma, and male breast cancer.

Obesity and Cancer Mortality

A growing body of evidence from observational studies has found that obesity is associated with poorer cancer outcomes among individuals with cancer. IARC also reviewed the relationship between body fatness and cancer recurrence and survival

after diagnosis [6] and found some limitations to the existing data, including variation in study design, setting, and when body fatness was measured in relation to the cancer diagnosis. Currently, the largest body of evidence addresses breast cancer survivors, whereas studies of survivors of other cancers was more limited and findings varied [6].

A recent systematic review and meta-analysis of 79 cohort studies including over 210,000 women with 41,477 deaths estimated that compared with normal-weight women (BMI 18.5–24.9 kg/m^2), those who were overweight (BMI 25.0–29.9 kg/m^2) or obese (≥30.0 kg/m^2) before diagnosis had statistically significant 11% and 35% increased risks for breast-cancer-specific mortality, respectively [9]. The risk of mortality associated with overweight and obesity was similar for patients with estrogen receptor (ER)-positive and ER-negative breast cancer [10].

Evidence for a role of obesity in survival from other cancers supports adverse outcomes with higher levels of obesity for endometrial, prostate, pancreatic, colorectal, hepatocellular, and ovarian cancer (limited to early-stage disease), as well as some hematologic malignancies [11, 12]. Though, as we will discuss later, overweight and obesity are at times associated better outcomes for certain cancer types. This has been seen for lung, esophageal, and kidney cancer and maybe, at least in part, due to the fact that these cancers are often associated with cachexia. It has been observed that these tumor types are more likely to be diagnosed at an advanced stage [11–13].

A growing number of observational studies have also observed an association between post-diagnosis weight gain and a higher risk of recurrence and mortality, independent of body mass index at diagnosis [14]. While IARC was not able to formally evaluate the association due to limited lower quality data, intentional weight loss in observational studies or from follow-up of patients undergoing bariatric surgery has been associated with reduced cancer risk, especially for breast and endometrial cancer [6]. However, not all results of observational studies of weight change have been consistent and the associations in these studies may be due to reverse causation. Therefore, randomized trials are needed to better address whether post-diagnosis weight loss in overweight or obese cancer survivors negates this adverse association between obesity and poor prognosis.

Body Composition

As mentioned earlier, most observational studies of obesity and cancer risk and mortality rely on BMI as a measure of obesity. Although BMI is correlated with obesity, it is an imperfect measure because it does not distinguish between the components of body composition, namely adiposity and muscle mass. Additionally, BMI does not fully reflect metabolic responses to excess weight and/or adiposity. Thus, some people with normal BMI have excess adipose tissue and metabolic abnormalities that are associated with poor health outcomes. These individuals have been considered to have metabolic obesity. Therefore, the use of BMI alone is a

suboptimal predictor of health outcomes and of metabolic factors that may be related to cancer risk and mortality.

As discussed earlier, higher BMI is positively associated with incidence and mortality of many cancers. Although it is important to note that BMI can also exhibit a null or U-shaped relationship with cancer risk and survival, with the lowest risk of cancer associated with the overweight BMI category (i.e., BMI: 25–29). This observation of overweight associated with improved survival is termed the "obesity paradox," [15] yet some argue the term "overweight paradox" or "BMI paradox" may be more appropriate. It is hypothesized that the shape of the association between BMI and cancer risk and survival may be determined by relationships with lean body mass and fat mass. Therefore, the "obesity paradox" controversy may be largely explained by low muscle mass, rather than low-fat mass, in the lower range of BMI (i.e., BMI <25) [16]. Low muscle mass may be important to understand in this relationship, as it is associated with higher risk of recurrence, overall and cancer-specific mortality, as well as surgical complications, and treatment-related toxicities [16]. When comparing individuals who are overweight or obese to those who are normal weight, those who are overweight/obese have higher levels of muscle on average [16].

A recent example of alternative measures of obesity was a study of dual energy x-ray absorptiometry (DXA) measures of obesity and the risk of breast cancer in a secondary analysis of 3460 postmenopausal women with normal BMI(18.5 to <25) enrolled in the Women's Health Initiative (WHI) [17]. Percentage of whole-body fat was associated with increased breast cancer risk; hazard ratio (HR) = 1.79 (95% CI, 1.14–2.83; $P = 0.03$) for the upper versus lower quartile of this measure [17].

More attention is being paid to body composition and cancer. Focus is being directed here, as sarcopenia (low muscle mass) has been associated with mortality across multiple disease stages and cancer types, as well as toxicity and surgery complications [18]. A limited number of studies have evaluated body composition measures from computed tomography (CT) in relation to mortality in breast cancer patients and have found sarcopenia associated with an increased risk of death [19–23]. Recently, Caan et al. reported that sarcopenia defined as skeletal muscle index <40cm^2/m^2 (measured by a single-slice abdominal cross-sectional area at the L3 vertebra) was associated with an increased risk of death (HR = 1.41; 95 % CI, 1.18–1.69) in patients with non-metastatic breast cancer [24]. This observation raises the possibility that muscle mass, in addition to fat mass, may provide important and novel information regarding the risk of cancer and cancer outcomes. In a meta-analysis of 38 studies, low muscle area assessed from clinically acquired CT was observed in 27.7% of patients with cancer and associated with poorer overall survival (HR = 1.44, 95% CI: 1.32–1.56) [25].

Future research should use new approaches to assess body composition, such as computed tomography, which provides more detailed information on the extent and location of adipose tissue (e.g., visceral, subcutaneous, and intramuscular), as well as muscle mass.

Guidelines for Lowering the Risk of Cancer Mortality Associated with Obesity

For achieving and maintaining a healthy weight, the American Cancer Society recommends following a dietary pattern that is high in vegetables, fruits, and whole grains, avoiding sugar-sweetened beverages and limiting the consumption of processed and red meats, as well as alcohol (Table 15.1) [26]. They also advise an exercise regimen that includes 150 min per week of aerobic exercise and at least two sessions of strength training exercise per week for cancer survivors and decreasing sedentary time. The physical activity recommendations are similar to the US Department of Health and Human Resources Physical Activity Guidelines and the American College of Sports Medicine recommendation for physical activity [27].

Adherence to the lifestyle recommendations on weight, nutrition, and physical activity has been associated with a reduced risk of total cancer incidence and mortality in prospective observational studies. For example, the VITAL study showed that breast cancer risk was reduced by 60% in women who met the WCRF/AICR recommendations, which are similar to the ACS recommendations, compared with those who did not meet the recommendations [28]. In another analysis of both men and women in VITAL, cancer-specific mortality was 61% lower among those who met at least five of the recommendations compared to those who did not meet any of the recommendations [29]. The Cancer Prevention Study-II (CPS-II) found a 24% and 30% lower risk of cancer mortality in 6613 women and 10,369 men, respectively, who adhered to the ACS lifestyle guidelines [30].

Despite these lifestyle recommendations being in place, a majority of cancer survivors are overweight or obese, and fewer follow the diet and physical activity recommendations. In the CPS-II, only 4% of women met all the lifestyle recommendations [30]. Similarly, in the DIANA trial, at baseline, only 7% of breast cancer patients with metabolic syndrome (and 13% of breast cancer patients without the metabolic syndrome) met the lifestyle recommendations [31]. The Iowa Women's Health Study observed that 34% of the 2193 female cancer survivors met the lifestyle recommendations [32] and while higher than some other studies, still less than ideal.

Table 15.1 Lifestyle guidelines

Physical activity guidelines
1. 150+ min/week of moderate to vigorous intensity physical activity or 75 min/week of vigorous-intensity physical activity.
2. Twice-weekly strength training.
3. Reduce sedentary time.
Dietary guidelines
4. Eat a combination of 5+ fruits and/or vegetables servings/day.
5. Reduce simple sugars.
6. Limit consumption of processed and red meats to ≤18 ounces/week.
7. Limit alcohol consumption to 1 drink/day or 8 drinks/week.

The reason for low adherence to lifestyle guidelines is likely multifactorial. It is very difficult to make lifestyle changes and this may be further complicated by lack of access and reimbursement to structured weight management and exercise programs. Data from large-scale randomized trials of weight loss are also currently lacking regarding the amount of weight which needs to be lost and/or specific lifestyle changes that need to be made to maximize reduction in cancer risk and mortality.

In 2014, the American Society of Clinical Oncology (ASCO) published a position statement on obesity and cancer, citing their commitment to reducing the impact of obesity on cancer through a multipronged initiative to increase education and awareness of the evidence linking obesity and cancer [11].

Mechanisms Potentially Mediating the Association Between Obesity and Cancer Outcomes

The link between obesity and cancer outcomes has strong biologic plausibility. The mechanisms, through which obesity could increase cancer risk and mortality, include changes in hormones involved in glucose and energy metabolism (e.g., insulin, leptin, and adiponectin), cellular growth factors (insulin-like growth factors and their binding proteins), steroid hormone metabolism, inflammatory mediators, DNA oxidative damage, and immune function [33–35]. To date, many studies among cancer survivors have relied on measures related to these potential mechanisms as surrogate markers of cancer risk, recurrence, and mortality when those definitive endpoints cannot be assessed.

Goodwin and colleagues demonstrated a three-fold increase in the risk of breast cancer mortality in patients within the highest quartile of fasting insulin levels compared to the lowest [36]. In addition to insulin, other growth factors and metabolic hormones, such as insulin-like growth factor-1, leptin, and adiponectin, have been associated with poor outcomes in patients with cancer. Chronic inflammation, also associated with obesity, has also been linked to cancer prognosis.

Other newer potential mechanisms of action and biomarkers under investigation include changes in proliferation (i.e., Ki-67) in benign or tumor tissue. Assessment of gene changes at the mRNA level including microRNA, tissue cytokine changes, or changes in key proteins in pathways, such as MAP kinase and mTOR, are also being explored [37, 38]. Other novel, understudied biomarkers include DNA methylation of cancer genes and small molecule metabolite levels.

Most recently, a weight control intervention in an obese mouse model in melanoma found that obesity restricted the accessibility of chemotherapy to tumor tissues [39]. Upon weight loss, the accumulation and efficacy of chemotherapy was improved. In vitro approaches suggest drug-resistance in obese mice. Thus, preclinical models suggest that obesity not only supports cancer progression, but also impairs chemotherapy outcomes, which can be improved with weight loss.

Energy balance interventions are also being conducted to examine the impact of healthy lifestyle behavior changes in diet and physical activity on adjuvant and

endocrine therapy adherence among cancer patients. It is hypothesized that favorable changes in diet and exercise may improve side effects and toxicity associated with treatment, in turn, improving adherence to treatment [40, 41].

There is growing interest in the interplay between adiposity, diet, and physical activity and the microbiome. Much of the microbiome research on body composition, to date, has focused predominantly on adiposity, with changes in adiposity impacting the gut microbiota of mice [42], and evidence that BMI is strongly related to the human gut microbiome [43, 44]. Furthermore, studies have demonstrated that the relative abundance of Bacteroidetes, a dominant bacterial phylum, in the human gut, is lower in those who are obese as compared to those who are lean, and relative abundance of Bacteroidetes tends to increase as individuals lose weight [45, 46]. There are a few human studies that have examined the relationship between weight-loss interventions and the gut microbiota, but these are largely restricted to studies of surgery-mediated weight loss. One study of 30 obese women who underwent bariatric surgery detected 58 bacterial genera, which were undetectable before bariatric surgery, in 6-month postsurgical fecal samples from all patients [47]. The results of this study and two smaller studies [48, 49] provide compelling evidence that microbial diversity increases after weight loss. However, it remains unclear if these changes are restricted to surgery-mediated or extreme weight loss.

Tying research on the microbiome together with carcinogenesis has also revealed that altered composition of the gut microbiota, including lower alpha-diversity (i.e., the number of taxa detected in the gut) was associated with postmenopausal breast cancer [50], as well as high non-ovarian systemic estrogen levels that contribute to postmenopausal breast cancer risk [51]. Kwa et al. also recently described the "estrobolome" as important in breast cancer, whereby intestinal bacterial genes capable of metabolizing estrogens might be associated with ER+ postmenopausal breast cancer [52]. Metabolites and numerous microbial metabolites, such as enterolactone, have been inversely associated with lower all-cause mortality, breast cancer-specific mortality, and disease-free survival among breast cancer patients [53].

Given the hypothesized and known mechanisms mediating the association between obesity and cancer, there is a need to identify energy balance interventions that can favorably change these mediators or surrogate markers. While this will not prove cause-and-effect, it can point to types of interventions that could have biological effects, and which would be most advantageous to test in a randomized clinical trial with disease-free survival endpoints.

Randomized Trials of Weight Loss on Cancer Outcomes

Trials on Surrogate Markers

A growing number of interventions have been conducted evaluating weight loss as a surrogate marker of cancer outcomes in cancer survivors, given the associations between BMI and cancer risk and mortality. Research has focused largely on breast cancer survivors. The majority of weight loss interventions have achieved over 5%

weight loss from baseline. A 10% weight loss goal had previously been adopted for many weight loss trials. However, a weight loss of 5% or more is considered clinically significant by the United States Preventive Services Taskforce (USPSTF) [54].

The Lifestyle Intervention Study in Adjuvant Treatment of Early Breast Cancer (LISA) by Goodwin et al. was a 2-year multicenter, telephone-based weight loss intervention in women with breast cancer [55]. The intervention entailed decreasing total energy intake (500–1000 kcal per day deficit) and attaining 150–200 minutes of moderate intensity physical activity per week to achieve up to a 10% weight loss (up to 10%). They observed a statistically significant 5.3% weight loss at 6 months in the weight loss group compared with a 0.7% weight loss in the control group. A statistically significant weight loss was sustained over 2 years (3.6% loss versus 0.4% loss), The original aim of LISA was to examine the impact of weight loss on disease-free survival; however, accrual was terminated after the enrollment of 338 of the 2150 planned participants because a loss of funding, leaving the clinically important questions of weight loss effect on breast cancer recurrence and mortality unanswered.

Irwin and colleagues conducted an in-person and telephone-based weight loss trial in 100 women treated for breast cancer [56]. This intervention also recommended dietary changes and increasing physical activity to achieve weight loss. Women who were randomized to intervention lost 6% body weight on average versus 2% in control subjects. This weight loss led to a 30% statistically significant reduction in C-reactive protein and nonsignificant 10% and 15% reductions in insulin and leptin, respectively.

Recently, Dieli-Conwright and colleagues examined the impact of a 16-week exercise trial on adipose tissue changes related to inflammation, specifically in white adipose tissues, in breast cancer survivors [57]. Exercise participants experienced significant improvements in body composition, cardiometabolic biomarkers, and systemic inflammation (all $p < 0.03$ versus control). Adipose tissues from exercise participants showed a significant decrease in pro-inflammatory M1 adipose tissue macrophages (ATM) ($p < 0.001$), an increase in anti-inflammatory M2 ATM ($p < 0.001$), increased adipose tissue secretion of anti-inflammatory cytokines such as adiponectin and decreased secretion of the pro-inflammatory cytokines IL-6 and TNF- α (all $p < 0.055$). Thus, suggesting that exercise attenuates adipose tissue inflammation in obese postmenopausal breast cancer survivors, though the small sample size limits conclusions from this trial.

Building off of clinically important research showing a benefit of supervised resistance training on breast cancer-related lymphedema [58], Schmitz and colleagues recently conducted a 4-arm trial of diet-induced weight loss, home-based exercise, the combination of weight loss and exercise versus control on breast cancer-related lymphedema in 351 breast cancer survivors experiencing lymphedema [59]. Despite clinically meaningful weight loss and high adherence to the home-based exercise, these lifestyle interventions did not improve lymphedema outcomes. Thus, supervised, facility-based exercise programs may be necessary for improving lymphedema. Some research has been conducted in relation to other cancer types. For example, a recent study examined weight loss in 44 men with

prostate cancer prior to radical prostatectomy to determine if weight loss affects tumor apoptosis and proliferation [60]. Overweight and obese men scheduled for radical prostatectomy were randomized to a 5–8-week weight loss program consisting of standard structured energy-restricted meal plans (1200–1500 Kcal/day) and physical activity or to a control group. The primary endpoint was apoptotic index in the radical prostatectomy malignant epithelium. Men randomized to the intervention group had significantly more weight loss (Intervention: -3.7 ± 0.5 kg; Control: -1.6 ± 0.5 kg; $p = 0.007$) than the control group; however, there was no significant difference in apoptotic or proliferation index between the groups. In addition, triglyceride and insulin levels were significantly decreased in the weight loss group compared with the control group.

Trials on Cancer Risk and Mortality

A large body of observational data supports a relationship between weight and cancer risk and mortality and preclinical trials and smaller biomarker trials, providing a biologic rationale for this relationship. However, there are little data regarding the impact of weight loss upon the risk of recurrence and mortality in those diagnosed with cancer from randomized controls trials. Given that weight is a modifiable factor, further research is needed to determine if weight loss could be an effective strategy to improve prognosis in overweight and obese men and women with cancer.

Diet trials on breast cancer risk and mortality have been conducted and weight loss trials in cancer survivors are underway and will provide definitive evidence as to whether lifestyle change will improve cancer outcomes.

Diet Trials

Two diet trials have been conducted among early-state breast cancer survivors addressing breast cancer recurrence and survival [61, 62]. Though the studies did not focus specifically on caloric restriction, they warrant review here. The Women's Healthy Eating and Living (WHEL) study was a multicenter trial conducted among 3088 women who had been previously treated for early-stage breast cancer [62]. The intervention involved a telephone counseling program, cooking classes, and newsletters to promote diet that included a daily diet of 5 vegetable servings plus 16 oz. of vegetable juice, 3 fruit servings, 30 g of fiber, and 15–20% of energy intake from fat. The primary study outcomes were recurrent and new primary breast cancer and all-cause mortality. The study followed women for 7.3 years and there was no reduction in breast cancer events or mortality. Over the course of the study, it was found that the groups differed by less than 80 kcal/d in energy intake and by less than 1 kg in body weight. Thus, if the effect of a dietary change on these outcomes would function through a weight change causal pathway, it is possible that the lack

of weight loss in the intervention group may partially explain the null finding. It was also noted that WHEL participants in both groups had a high fruit and vegetable intake at baseline, such that it may have been difficult to detect differences across the groups due to diet composition changes.

The Women's Intervention Nutrition Study (WINS) did observe a statistically significant modest difference in weight loss and observed a reduction in breast cancer recurrent among those in the intervention groups compared to the usual diet group after a median follow-up of 5 years [61]. These effects were stronger in the subgroup of estrogen receptor negative tumors. The intervention group targeted a low-fat diet (15% of total energy intake) and provided individual counseling to participants from registered dietitians.

A third trial focused on diet and breast cancer was the Women's Health Initiative (WHI) Dietary Modification trial, though the primary outcome was breast cancer risk among 48,835 women without a history of the disease [63]. The intervention sought to reduce fat to 20% of total energy intake as well as increase fruit, vegetable, and grain intake. The intervention group had a modest statistically significant 3% weight loss after 1 year. Though the main intervention findings for a low-fat diet on the risk of breast cancer after a median of 8.5 years of follow-up were suggestive of an inverse association, the results were not statistically significant. With continued follow-up (16.1 years), a recent analysis found deaths after breast cancer were significantly reduced in the intervention group [64]. There was also a reduction in deaths from breast cancer, but this was not statistically significant. These effects were not altered with adjustment for weight change.

As research studies on energetics and cancer outcomes continue, diet may be an important component to attaining weight loss in lifestyle interventions. While the existing studies were not designed for weight loss, data from these point to the importance of weight change for cancer survivors. Additionally, diet quality, independent of physical activity and BMI, may also be relevant to cancer outcomes, as a recent meta-analysis found higher diet quality associated with lower overall mortality in cancer survivors [65].

Ongoing Weight Loss and Lifestyle Trials

The Breast Cancer Weight Loss (BWEL) study is an ongoing study designed to test the impact of a 2-year telephone-based weight loss intervention on invasive disease-free survival in 3136 women with stage II-III, HER-2 negative breast cancer who have a body mass index (BMI) of at least 27 kg/m^2 [66]. Secondary outcomes of the trial include the impact of the weight loss intervention on overall survival, body weight, physical activity, dietary intakes, incidence of comorbidities, serum biomarkers, and patient-reported outcomes. The intervention content is based on the Diabetes Prevention Program, Look Ahead, and LISA and has a weight loss goal of 10% based on caloric restriction and increased physical activity. The intervention entails 42 telephone calls, delivered by health coaches based at the Dana-Farber

Cancer Institute. Calls are supplemented by an intervention workbook, as well as a number of tools to help facilitate weight loss.

The SUCCESS C trial is another lifestyle intervention on women with breast cancer with an evaluation of disease-free survival [67]. This study has enrolled 2292 women with a BMI of 24 or higher who were diagnosed with HER2-negative early-stage breast cancer and were treated with one of two chemotherapy regimens. Results should be forthcoming in the next couple of years.

Another ongoing study called LIVES [68] involves a 24-month lifestyle intervention in relation to progression-free survival after oncologic therapy for stage II-IV ovarian cancer. Women are randomized 1:1 to a high vegetable and fiber, low-fat diet with daily physical activity goals or an attention control group. Secondary outcomes to be evaluated include QoL and gastrointestinal health.

In summary, a favorable finding from these and other future energy balance interventions in relation to survival would likely influence the number of clinicians recommending weight management through diet and/or exercise. Additional data relevant to cancer outcomes would also improve the landscape of reimbursement of lifestyle programs, especially given that lifestyle behaviors are associated with improved quality of life and reduced comorbidities.

Other Cancer Outcomes Examined in Weight Loss Trials in Cancer Survivors

In the absence of convincing information regarding the beneficial effects of weight management, healthy eating, and exercise on recurrence or death, we can look to the impact of these factors on general health, reduced toxicity and fatigue, enhanced physical functioning, better quality of life, and lower risk of diabetes and cardiovascular disease among cancer survivors. All of these additional outcomes can provide important potential benefits to survivors.

A growing number of studies have examined the effects of exercise on cardiovascular disease in cancer survivors, with a review indicating that exercise improves cardiorespiratory fitness—a powerful predictor of mortality [69]. Growing evidence and numerous systematic reviews and meta-analyses also suggest that exercise may improve quality of life in patients treated for cancer [70–73].

In a randomized controlled trial entitled RENEW (Reach-out to Enhance Wellness), which promoted increased physical activity, a healthy diet, and as low rate of weight loss among 641 older, overweight, and obese long-term cancer survivors, of which 45% (n = 289) had been diagnosed with breast cancer, Morey and colleagues found that at 12-month follow-up, mean physical function scores declined less rapidly in the intervention arm (−2.15; 95% confidence interval [CI], −0.36 to −3.93) than in the control arm (−4.84; 95% CI, −3.04 to −6.63) (p = 0.03) [74]. Moreover, changes in the intervention arm were significantly more favorable in terms of lessened pain and enhanced vitality, overall health, social functioning, mental health, and physical and emotional roles.

Results from the ENERGY weight loss trial conducted in 692 breast cancer survivors found improvements in physical function [75]. However, differences in vitality were not as strong and only reached borderline significance; moreover, between-arm differences in quality-of-life components diminished more rapidly over time, rather than being largely sustained over the 2-year study period.

Research Gaps in Regard to Socioeconomic Status, Race/Ethnicity, Age, and Geography

A workshop convened by the National Cancer Policy Forum of the National Academies of Sciences, Engineering, and Medicine in 2017 discussed multiple issues related to obesity and cancer and identified some key gaps in the current research [72]. Below, we highlight the areas identified by this recent workshop that brought together experts in energetics and cancer. The opportunities, for additional work they discussed, included expanding research into certain populations of cancer survivors with a focus on several key groups that have a higher burden of cancer, namely cancer survivors who are low-income, minority, older, or living in rural settings [72]. Compounding this issue is the fact that these individuals are also more likely to be inactive, overweight or obese, and suffer some other comorbid chronic conditions.

As mentioned early, much of the energy balance research, particularly interventions in cancer survivors, to date, has focused on breast cancer and even when addressing other cancers, studies have largely enrolled non-Hispanic whites. Therefore, research is needed to develop culturally appropriate weight loss interventions in a diverse range of populations to assess how these can potentially benefit a wider swath of cancer survivors [72]. This includes not only survivors of racial and ethnic minorities, but also those from different socioeconomic backgrounds. This work is critical to not only address the needs of these survivors but also reduce disparities in cancer outcomes.

Existing research, among racial and ethnic minority cancer survivors, had been limited by small sample sizes as well as quasi-experimental designs, and most have been conducted among only breast cancer survivors [72]. While these studies have helped to establish important issues related to feasibility, much can be done to expand upon this area, including assessing biomarkers and address other cancer types. Encouragingly, many of the studies have found favorable changes on outcomes, such as weight loss, behavior changes, and quality of life indicating the great potential for future work in these populations.

One study of a lifestyle intervention in an understudied population was conducted by Stolley and colleagues. They examined the effects of Moving Forward, a weight loss intervention for African American breast cancer survivors on weight, body composition, and behavior [76]. Women were randomly assigned to a 6-month interventionist-guided (n = 125) or self-guided (n = 121) weight loss program

supporting behavioral changes to promote a 5% weight loss. Both groups lost weight. Mean and percentage of weight loss were greater in the guided versus self-guided group; 44% in the guided group and 19% in the self-guided group met the 5% goal. This study supports the efficacy of a community-based interventionist-guided weight loss program in African-American breast cancer survivors.

In addition to addressing the minority cancer survivors, there is a need for energy balance research among both older and younger cancer survivors [72]. Approximately 64% of cancer survivors are 65 years and older, and by 2040 older survivors are projected to make up 74% of survivors [3]. Recent estimates indicate there are 429,000 childhood cancer survivors and more than 80% of children with cancer survive 5 years or more [3, 77]. There are also an estimated 70,000 adolescent and young adult cancer survivors [3, 77]. In both of these groups of cancer survivors, there is a strong need to research the side effects of cancer and their treatment [72]. Given the increased risk of cardiovascular disease, second cancers, osteoporosis, metabolic syndrome, fatigue, cognitive changes, and sarcopenia in these survivors, these two groups could potentially benefit from lifestyle energy balance interventions.

Rural cancer survivors are also understudied in the existing energy balance research. They have higher cancer mortality rates, comorbidities, obesity, and physical inactivity than their urban counterparts [72], suggesting an opportunity for interventions that improve outcomes.

As the field moves forward, expanding research in the groups identified above will help to ensure that energy balance intervention associated with better outcomes can benefit a larger group of cancer survivors. In addition, since these populations may have a lower prevalence of many of the lifestyle recommendations related to diet and physical activity, there may be an even greater chance for interventions to have measurable effects. Tailored interventions developed with input from these populations and key stakeholders are key to ensure short- and long-term success.

Implementation of Energy Balance Interventions in Clinical Care

Physical activity and weight management have not traditionally been a part of cancer treatment or cancer survivorship programs. Given that programs targeting these factors carry a tremendous potential to affect the length and quality of survival in a positive manner and prevent or control morbidity associated with cancer or its treatment, oncologists and primary care physicians should be encouraged to counsel cancer survivors proactively about exercise and weight management.

As a result of the strong effect of lifestyle changes on diabetes prevention in the Diabetes Prevention Program (DPP) trial, certain YMCA facilities across the country offer a modified version of the DPP program. Additionally, certain YMCAs across the country offer the LIVESTRONG at the YMCA program, which is a free 3-month exercise program for cancer survivors [78].

In general though, for adults with obesity, the USPSTF recommends obesity behavioral interventions that entail 12–26 visits over the course of a year [54]. However, few providers have been trained in the delivery of behavior change therapies; and, currently, few major insurance plans provide reimbursement for the duration of care recommended by the USPSTF. Counseling for obesity is also typically underutilized. Lack of utilization may involve limited access to care, time constraints of primary care physicians, as well as a lack of training available for learning to deliver effective behavioral counseling.

Future Directions of Energy Balance and Cancer Research and Clinical Care

The immediate priorities for research related to obesity, energetics, and cancer outcomes include the need for information on the amount of weight loss and exercise likely to result in reduced cancer risk and mortality; more research in minorities, rural populations, and varied age groups; cost-effective methods for delivering energy balance interventions; and surrogate markers strongly associated with cancer risk and mortality. There is also a need to expand research to include different cancer sites and address the effects of energetics on newer cancer therapies.

Further, a more detailed elucidation of the contributions of body composition to cancer risk and mortality will be important to help identify those most at risk for poorer outcomes and to inform preventive strategies. Data also support the inclusion of sarcopenia, along with adiposity and BMI, as standard oncological markers.

Lastly, future studies should explore what factors influence weight loss success in various cancer types. Overall, the limited number of well-powered randomized trials in cancer survivors highlights the need for future studies to determine whether weight loss, and which components of weight loss interventions, in cancer survivors (or those at high risk) improves cancer outcomes.

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Chapter 16
Advanced Cancers, Metastatic Disease, and Palliative Care

Sonya S. Lowe, Christopher Sellar, Kirsten Suderman, and Margaret L. McNeely

Introduction

Approximately 50% of all individuals with a cancer diagnosis will ultimately die from disease progression [1]. The World Health Organization endorsed palliative care as a global health issue in 1990 and defined palliative care as "the active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems, is paramount. The goal of palliative care is achievement of the best possible quality of life for patients and their families" [2]. In parallel with the rising incidence of cancer and improved treatment, there is a growing population of survivors living months to years longer with advanced chronic cancer, survivors who are not yet palliative or appropriate for end-of-life care. Maintaining function and control of symptoms is necessary for these survivors to *live well* for as long as possible [3].

Timely rehabilitation and exercise, at appropriate volumes, shows promise as a strategy to optimize functional capacity, symptom management, independence, and quality of life (QoL) [3–5]. Evidence suggests that exercise may help to prevent or delay declines in aerobic fitness and strength, and maintain adequate physical

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Table 16.1 Key terms and definitions

Key term	Definition
Survivor	Any person with cancer, from the time of cancer diagnosis, through the balance of their life [160]
Palliative care	The active holistic care of individuals across all ages with serious health-related suffering due to severe illness and especially of those near the end of life. It aims to improve the quality of life of survivors, their families, and their caregivers [11]
Advanced cancer	Incurable malignant disease [13]
Metastatic disease	Spread of cancer cells from the primary tumor to other parts of the body, by means of the blood or lymphatic system [19]
End of life or terminal cancer	Life-limiting malignant disease with irreversible decline and expected survival in terms of months or less [23]

function to perform daily activities [3]. Moreover, performance status, which is used to guide decision-making regarding appropriate treatment for survivors with advanced cancer, heightens the importance of exercise to maintain or attenuate declines in function and quality of life [6]. The purpose of this chapter is to outline the role of exercise in survivors with advanced cancer, who have metastatic disease, or who are receiving palliative care. Our aim is to focus on the unique needs of these survivors and to highlight the differences in terms of exercise screening, testing, and training from those of survivors with curative disease. Table 16.1 includes the definitions for the terms survivor, palliative care, advanced cancer, metastatic disease, and terminal (end of life) cancer.

Palliative Care

Modern definitions of palliative care are reflective of the ever-changing landscape of how palliative care is delivered worldwide. Whereas traditional models of palliative care were focused on caring for survivors solely in the terminal stage of illness, there is a proliferation of evidence in support of integration of palliative care early in the disease trajectory [7]. In their 2018 Cochrane review of seven randomized and cluster-randomized controlled trials involving a total of 1614 participants, Haun et al. showed that early palliative care interventions had beneficial effects on quality of life and symptom intensity in survivors with advanced cancer, compared to usual/standard cancer care alone; despite small effect sizes, these findings were felt to be clinically relevant in survivors with advanced stage disease and limited prognosis [8]. In their 2017 updated Clinical Practice Guideline, the American Society of Clinical Oncology recommends that advanced cancer survivors receive dedicated palliative care services, early in the disease course and alongside active treatment of their cancer; early palliative care involvement was defined as within 8 weeks of the initial diagnosis of advanced cancer [9].

In response to the growing evidence base, the 2017 Lancet Commission argued for a new definition that "explicitly rejects any time or prognostic limitation on access to palliative care, includes complex chronic or acute, life-threatening, or life-limiting health conditions, and considers all levels of the health-care system from primary to specialized care and all settings where palliative care can be delivered" (p. 1400) [10]. Hence, the International Association for Hospice and Palliative Care (IAHPC) developed its own international consensus-based definition of palliative care, which is the "active holistic care of individuals across all ages with serious health-related suffering due to severe illness, and especially of those near the end of life" with the overall aim of improving quality of life for survivors, caregivers, and families [11]. The IAHPC contends that palliative care is applicable throughout the course of an illness, can be provided concurrently with disease modifying therapies, and can positively influence the course of illness.

Advanced Cancer

Differentiating between the concepts of advanced, metastatic, and terminal (end of life) disease remains challenging [12]. The American Society of Clinical Oncology defines advanced cancer as incurable, malignant disease [13]. This definition is congruent with that of the National Cancer Institute, for whom advanced cancer is "cancer that is unlikely to be cured or controlled with treatment" [14]. The proportion of cases of advanced cancer at diagnosis for lung cancer, for example, is approximately 75% [15]. Other reported cancers with high proportions of advanced cancers at diagnosis include pancreatic cancer (79%) and non-Hodgkin's lymphoma (64%) [15]. There are clinical circumstances, however, for which these definitions do not apply. Locally advanced cancer, or cancer that has grown beyond its initial primary site but has not yet spread to distant sites in the body, may be curable, depending on the cancer primary [16]. For example, many locally advanced prostate cancers are curable [17], whereas most locally advanced pancreatic cancers are not curable [18].

Metastatic Disease

The Canadian Cancer Society defines metastatic cancer as the "spread of cancer cells from the primary tumor to other parts of the body, by means of the blood or lymphatic system" [19]. This definition is congruent with that of the National Cancer Institute, for whom metastatic cancer is "the spread of cancer cells from the place where they first formed to another part of the body" [20]. Metastasis involves breakdown of intercellular cohesion, tumor cell migration, angiogenesis, access to and survival in the systemic circulation, evasion of local immune responses, and growth in distant organs [21]. Again, there are clinical

circumstances wherein metastatic cancer may not necessarily imply incurable or terminal disease. For example, greater than 80% of cases of metastatic testicular cancer are curable [22].

Terminal Disease

There is significant ambiguity and a lack of definitional clarity in the terms "actively dying," "end of life," "terminally ill," and "terminal care" [12]. In their 2014 systematic review, Hui et al. highlighted the key defining features of the terms "end of life," "terminally ill," and "terminal care," as being "life-limiting disease with irreversible decline and expected survival in terms of months or less" [23]. There are clinical circumstances, however, where terminal cancer implies neither advanced nor metastatic disease. For example, survivors with high-grade gliomas may have terminal disease and no metastases [24].

Research Evidence Supporting Exercise

Emerging evidence supports the benefits of exercise for survivors with advanced cancers [3, 25, 26]. The number and quality of studies looking at the relationship between exercise and advanced cancer have greatly increased in number over the last decade. Three recent systematic reviews have been performed examining the benefits of exercise in advanced cancers (Table 16.2); these reviews comprised 23 distinct randomized controlled trials (RCTs) and a total of 1787 participants. Of these 23 RCTs, 9 studies were performed with mixed cancer types, 5 with lung cancer, 4 with hematological cancers, 2 with breast cancer, 1 with gastrointestinal cancers, and 2 studies involved survivors with bone metastases. The heterogeneity among studies in tumor types, definitions of advanced or terminal cancer, inclusion criteria, and exercise prescription variables precludes synthesis of findings, thus limiting overall conclusions on benefits. In general, however, findings support feasibility of exercise as assessed by safety (e.g., no serious adverse events), recruitment and completion rates, and adherence (e.g., attendance). The most important findings include improvements in cardiopulmonary fitness, muscle strength, and physical function [3, 25]. The benefits of exercise alone for quality of life and symptoms such as fatigue and dyspnea remain unclear. However, studies involving interdisciplinary rehabilitation interventions, for example, have shown benefit for fatigue [27, 28], chemotherapy-induced peripheral neuropathy [29], body weight management [30], and quality of life [30].

Given the heterogeneity among trials to date, more research is needed to explore the optimal regimen in terms of the stage of disease (advanced, metastatic, or end of life), as well as exercise mode and parameters of frequency, intensity, time, and type. Studies, to date, have mostly involved supervised exercise programs.

Table 16.2 Systematic review evidence

Author, year, and definition	# of studies/ sample size/ designs	Feasibility measures	Main findings	Negative or unclear findings
Dittus, 2017 [3] "At least one third of the sample population had advanced cancer"	26 studies (N = 2038) 14 RCTs 10 pre/post 3 program evaluation	Recruitment: 26–86% Attrition: 11–54% Attendance: 65–95%	Cardiorespiratory fitness: 14/19 studies reported significant improvement; magnitude: +9.1% improvement Muscular strength: 11/12 studies significant: +7.6% Physical function: 9/9 studies reported significant improvement	Fatigue Quality of life
McIntyre, 2019 [25] "advanced lung cancer"	6 RCTs (N = 221)	No serious AE 8 minor Adverse Event (AE)	Exercise capacity as measured by 6-minute walk distance: mean difference 63.33 m; 95% CI 3.70–122.96; three studies, 59 participants	Dyspnea Quality of life
Heywood, 2017 [26] "cancer that is unlikely to be cured"	25 studies (N = 1088) 16 RCTs 9 cohort studies	6 minor AE Adherence: 65–89% Attendance: 59–100%	Safety and feasibility of general programs across cancer tumor groups	Optimal exercise parameters unclear (i.e., frequency, intensity, time, and type)

Home-based exercise is an attractive option for survivors with advanced cancer given advantages of time, eliminating the need for travel, and favoring activities of daily living; however, concerns exist over the feasibility of this type of programming [31, 32]. Wearable activity monitors, smartphone applications, and virtual interventions show promise as e-health solutions for the delivery of supported home-based interventions that also allow for exercise supervision and survivor (and caregiver) connectedness [33].

Goals of the Prescribed Physical Activity or Exercise Program

For survivors living with advanced, metastatic, or terminal cancer, exercise goals are often quite different from those with early-stage curative disease [34]. Symptom control, physical function, and maintenance of independence are primary reasons for seeking out and taking part in exercise interventions [3]. Exercise has the potential to improve function even if the disease is advanced; however, the focus of exercise may vary by the cancer type, the survivor's physical fitness and functioning, presenting impairments related to cancer or cancer treatment, and the presence of other illnesses or conditions. A survivor with advanced lung cancer, for example, may struggle with shortness of breath on

exertion limiting activities of daily living, while a survivor with a brain tumor may have deficits in balance, placing them at risk of falling. Thus, exercise programs need to be personalized and flexible. Moreover, exercise goals may need to be revisited periodically as the treatment approach changes, and the disease progresses. Importantly, the exercise professional must be able to recognize issues and determine how best to modify the exercise program as the survivor's situation changes [5]. Outside of the physical and functional goals of exercise, making the most of the potential psychosocial benefits from exercise participation should be considered, particularly the benefits of social interaction with other survivors in a group exercise setting.

For advanced cancer survivors with stable disease who are not receiving active treatment, the goals of exercise training may be to maintain or improve fitness and function, as well as to manage any effects of the disease and its prior treatments. Exercise during this period can also be used as a *prehabilitation* strategy to optimize performance status in preparation for future cancer treatments, that may be necessary either prophylactically, or to address eventual disease progression.

The goal of exercise for survivors with terminal cancer and limited life expectancy is to help maintain independence as the focus of care shifts to living as well as possible in the short term. At this stage, an interdisciplinary approach is paramount to address symptom management, and consideration should be given to integrating exercise into activities of daily living.

Screening for Exercise Testing and Participation

The goal of exercise screening in survivors with advanced cancer is to reduce the risk of any adverse events during fitness assessments or exercise training [35]. Screening of the survivor is important to identify existing risks related to exercise and should include a medical history covering the cancer diagnosis, current disease status and prognosis, treatment received and in process [36, 37], presenting impairments, and other potential comorbid conditions [38]. The screening process allows the exercise professional to (i) anticipate potential side effects and adverse events; (ii) identify the appropriate level of exercise supervision; (iii) identify the type of monitoring needed during exercise sessions; and (iv) identify the optimal type and intensity of exercise.

Suggested steps for screening and communication around exercise safety are outlined in the Screening and Triage Decision Tree in Fig. 16.1. We recommended that medical clearance be obtained prior to the survivor beginning an exercise program. This clearance should be sought from health care providers (HCP) who provide cancer care (e.g., oncologist, palliative care specialist) and/or who manage comorbid conditions (e.g., family physician, cardiologist). Any pre-exercise evaluation completed as part of the medical clearance is at the discretion of the medical provider and may include a physical examination, medical imaging, and/or laboratory tests [36]. Comprehensive screening, as outlined in Fig. 16.1, can effectively

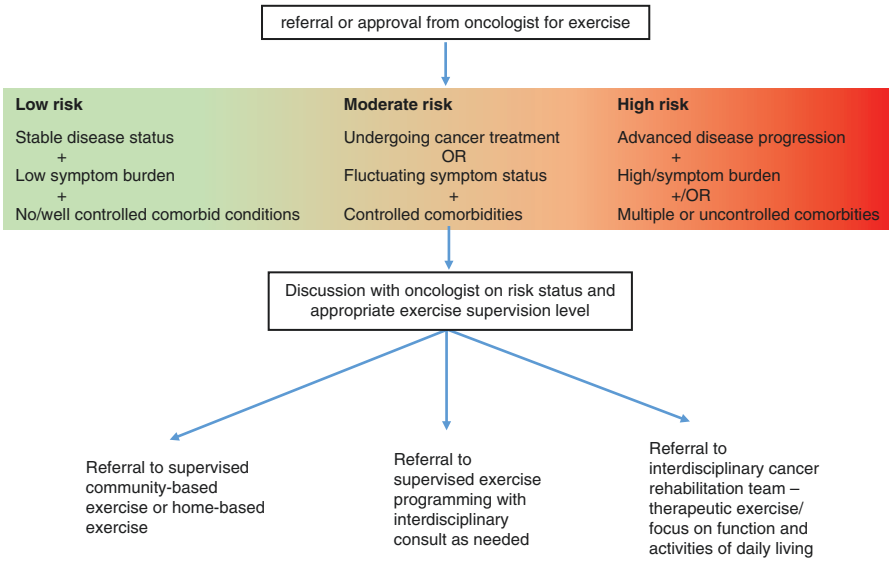

Fig. 16.1 Screening and triage to appropriate exercise programming

determine the most appropriate treatment pathway. For example, higher-risk or more complex individuals, or those experiencing severe or multiple cancer-related adverse effects, may require interdisciplinary cancer-specific rehabilitation support.

Objective Physical Fitness Assessment

Ideally, all aspects of health-related fitness should be assessed prior to the survivor beginning an exercise program including testing aerobic fitness, muscular strength, flexibility, and balance. Functional assessments such as the Timed Up and Go test, sit-to-stand, or Short Physical Performance Battery can easily be performed in the clinical setting and are helpful to inform the survivor's ability to carry out activities of daily living [39, 40]. A number of factors related to the survivor's status should be considered when selecting tests, such as functional status, cancer and treatment status, and the presence and extent of any comorbid conditions. These factors should be matched with the abilities, effort, and overall demand to complete the selected fitness assessments. Moreover, the overall goals of the exercise training program should be taken into account to determine what information is actually needed for effective exercise prescription, with tests then selected to match the needs and goals of the survivor. While gold standard, maximal type fitness assessments can be safely completed in individuals with advanced cancer [41, 42], when considering which tests to complete, the focus should be on avoiding any undue risk or burden to the survivor while still producing sufficient and accurate information to assist in the

exercise prescription and to monitor changes over time. Depending on the survivor's status, additional rest time between fitness tests and spreading the assessments over multiple days may be necessary.

Additional Special Tests and Monitoring

The physical assessment of the survivor with advanced cancer should start with assessment of vital signs [43]. For a survivor whose status may fluctuate on a daily basis (i.e., on treatment or with active progressive disease), we recommend monitoring of key vital signs at each visit. These resting physiological measures include heart rate, blood pressure, respiratory rate, and oxygen saturation; however, consideration should be given to incorporation of additional measures to monitor symptoms, as indicated [36]. For example, it may be useful to obtain heart rate and blood pressure readings in the supine, sitting, and standing positions for a survivor reporting symptoms of dizziness. This information can inform fall risk and the need for modifications in positioning of exercises (e.g., upright positions versus on a floor mat), the order of exercises (e.g., avoiding unnecessary or minimizing the number of position changes), and teaching the survivor strategies to move safely when changing positions (e.g., slowly changing position and pausing with each position change to allow for adaptation).

Body weight changes also have implications on the ability of the survivor to participate in and gain benefit from exercise. Gains in fat mass, and losses in muscle mass related to prescribed corticosteroids, for example, may negatively impact function and increase fall risk. A survivor with advanced cancer may become cachexic, leading to poor exercise tolerance and increased post-exercise fatigue [44]. Across cancer types, negative changes in body weight and composition add complexity to the survivor's programming and necessitate close collaboration with the dietician as well as the interdisciplinary team [18]. Furthermore, collaboration with specialists in physical medicine and rehabilitation and/or physical therapy may be needed for assessment and treatment of other impairments such as peripheral neuropathy; lymphedema; gait, ambulation, and fall risk and to address comorbid conditions such as arthritis.

Principles of Exercise

Many of the guiding principles of exercise prescription hold true in the advanced cancer exercise setting, with the most important considerations being individualization, progressive overload, specificity, and recovery [45]. Individualization of the exercise prescription to the survivor's current status, and modifying the program to match any change, is crucial to safe and beneficial exercise. The training overload (total volume of training), with FITT parameters of Frequency, Intensity,

Time/duration, and Type of training, should be considered, as would normally be done in other populations [36]. Progression of the total training volume should be gradual and symptom-limited and is best guided by the survivor's response to training. Determining the appropriate overload and progression of exercise is a challenge in the advanced cancer setting, as cancer treatments and disease progression may have a profound effect on physiological systems [46]. Specificity of the training program should address areas of need or weakness as determined from the initial screening and fitness assessment. Incorporating longer rest time between exercises and sets is important to avoid exacerbating symptoms such as fatigue, and the number of planned training sessions per week should allow for adequate rest and recovery, while also considering the time burden of appointments.

While currently available exercise guidelines for cancer survivors provide a reasonable framework for exercise prescription, a survivor with advanced cancer may need and prefer to exercise at lower total volumes and intensities of exercise [41, 47]. Applying the principles of exercise training and prescription becomes even more complex as disease and treatment factors tend to have a greater and growing impact on the survivor's ability to both complete and recover from exercise training. Ideally, some combination of aerobic, resistance, core, balance, and flexibility exercises should be included in the training program to benefit all aspects of the survivor's health-related fitness and functional abilities. We recommend that setting of intensities be conservative, particularly when the ability to prescribe specific training intensities (e.g., % maximum heart rate or one repetition maximum) is not possible from data obtained from the fitness assessment. The survivor should finish exercise sessions feeling better, possibly more energized or comfortably tired, and not be exhausted, or require a nap. Depending on the survivor's presentation and risk for adverse events, exercises that are high impact, high intensity, and/or of longer duration may need to be avoided [46]. The goal of the exercise prescription overall is to create a balance between having a sufficient exercise stimulus to positively impact the health and fitness of the survivor and not increase fatigue, cause pain or injury or exacerbate symptoms. The survivor's function, symptoms, or the disease itself may ultimately limit progression of exercise, and, in fact, the survivor do better with dose reduction over time.

The need for ongoing modification of programming should be anticipated to ensure that exercise participation is safe and effective. Each training session should begin with a conversation with the survivor regarding the response to the previous workout in terms of impact on fatigue and symptoms (immediately post-exercise and 24 and 48 hours later) to determine any immediate need for modifications to programming. Further, the survivor must understand the need to communicate any concerns during sessions to allow for in-training modifications. The perceived exertion scale is helpful for monitoring both exercise intensity and symptoms (e.g., dyspnea, fatigue, pain scales) [48]. The exercise professional should explain the proper use of the rating of perceived exertion scale at the commencement of the survivor's programming. Once trained and practiced, the survivor can effectively perceive their level of exertion, muscle fatigue, pain, or breathlessness [49]. Close attention to the survivor's perceived exertion can help to determine if the training volume is

set at a manageable level. Given the survivor's potential fluctuating status, this information is beneficial to also obtain feedback on perceived exertion when performing activities of daily living [49].

Exercise Professional Training

Exercise professionals should have adequate cancer education and experience to ensure the safety of the survivor and quality of exercise programming. Professionals with certifications, such as the Canadian Society of Exercise Physiology – Certified Exercise Physiologist and American College of Sports Medicine (ACSM) Clinical Exercise Physiologist, have the ideal combination of education and experience and approved scope of practice to work with survivors with advanced cancers [36]. Additional cancer-specific practical experience or formal training, such as ACSM/American Cancer Society Certified Cancer Exercise Trainer, is recommended. Other health professionals (medical doctors, nurse practitioners, physical therapists, and other rehabilitation staff) working with cancer survivors who also have experience or training in exercise are well suited to deliver exercise training in an advanced cancer setting.

Special Considerations

Cancer-Related Fatigue (CRF)

Cancer-related fatigue is a symptom subjectively experienced as a physical, emotional, and/or cognitive tiredness or exhaustion secondary to cancer or cancer treatment, which interferes with usual functioning, and that is distressing, persistent, and not proportional to recent activity [50]. There is wide variability in the clinical presentation of cancer-related fatigue, whose underlying pathophysiology is multifactorial and involves somatic, psychosocial, cognitive, and emotional variables [51]. Originating in the central nervous system, central fatigue presents as the inability to complete physical and mental tasks requiring self-motivation and internal cues, in the absence of motor weakness or cognitive failure [52]. Putative central mechanisms include the vagal afferent nerve [53], dysregulation of cytokines [54] or serotonin [55], and disruption of circadian rhythm [56] or the hypothalamic-pituitary-adrenal axis [57]. Peripheral fatigue, on the other hand, presents as the inability of muscle to perform a task in response to central stimulation, either at the level of muscle or the neuromuscular junction [58]. Putative peripheral mechanisms include adenosine triphosphate dysregulation [59], contractile properties [60], and muscle metabolism [61].

Fatigue is the most common and distressing symptom. A common physical complaint of CRF is the onset of tiredness and/ or weakness upon sustained exertion or

during repetitive tasks [62, 63]. Cancer-related fatigue occurs in up to 40% of survivors at the time of cancer diagnosis, in up to 80% of survivors treated with chemotherapy, and in up to 90% of survivors treated with radiotherapy [64]. In a systematic review of symptom prevalence in older cancer survivors receiving palliative care, fatigue was the most prevalent symptom, occurring in at least 50% [65]. Cancer-related fatigue negatively impacts activities of daily living and overall quality of life [63] and affects survivors more and for longer than any other symptom, including pain [66]. In a systematic review of symptoms associated with cancer-related fatigue, psychosocial distress had higher overall correlations with cancer-related fatigue than symptom distress [67].

Cancer-related fatigue management starts with comprehensive assessment of the symptom, its impact on the survivor's experience, and treatment of any potential contributors. Uncontrolled symptoms, such as pain, dyspnea, nausea, anxiety, and depression, can exacerbate fatigue in the cancer survivor [68]. Deconditioning due to prolonged bed rest and immobility, overexertion, infection, anemia, autonomic dysfunction, cachexia, polypharmacy, hypoxia, dehydration, metabolic/endocrine disorders, and renal/hepatic/cardiac comorbidities can all further contribute to symptoms of fatigue [69].

Commonly used pharmacological agents for the management of cancer-related fatigue include corticosteroids, megestrol acetate, psychostimulants, and investigational agents (e.g., eicosapentaenoic acid, thalidomide, L-carnitine, testosterone, melatonin) [70]. Non-pharmacological strategies for the management of fatigue include psychological interventions, physiotherapy, and occupational therapy [71]. The survivor with moderate to severe CRF may benefit from involvement of the interdisciplinary rehabilitation team where interventions may include, for example, nutrition counseling and occupational therapy education on energy conservation and maximization. For the exercise specialist, careful attention to symptom flares and excessive post-exercise fatigue allows for adjustment of the exercise prescription [72, 73]. With appropriately prescribed exercise, and monitoring of perceived exertion to inform activity pacing, the survivor should notice improved ability to complete daily tasks and meaningful activities, even if overall fatigue persists [73]. In a meta-analysis comparing pharmacological, psychological, and exercise treatments for cancer-related fatigue, exercise and psychological interventions were shown to be effective in reducing cancer-related fatigue both during and after cancer treatment and were significantly better than the available pharmacological options [74].

Bone Metastases

Bone is the third most frequent site of metastasis, after lung and liver. Bone metastases are nearly always multiple, and their distribution within the axial skeleton is primarily attributed to the red bone marrow therein. Although the overall incidence of bone metastases is not known, the incidence of bone metastases is highest in

Table 16.3 Imaging for bone metastases

Diagnostic imaging method	Detection and evaluation of bone metastases [161, 162]
X-ray	30–50% of bone destroyed before lesion is visible on x-ray; if lesion is present can inform stability of lesion
Bone scan	Detection of metastatic lesions
Computer tomography (CT)	Detection of metastatic lesions Visualization of trabecular and cortical bone integrity
Single-photon emission computed tomography with CT (SPECT-CT)	Bone metabolism Visualization of trabecular and cortical bone integrity
Positron-emission tomography combined with computed tomography	Bone metabolism with high sensitivity and specificity Visualization of trabecular and cortical bone integrity Metastases in other organ systems
Magnetic resonance imaging with or without contrast	Visualization of bone marrow involvement Visualization of tumor extension beyond bone Determination of the extent of spinal involvement – relation of lesion to the spinal cord and adjacent structures

multiple myeloma (up to 95%), followed by prostate cancer (up to 90%), breast cancer (up to 75%), lung cancer (up to 64%), thyroid cancer (60%), melanoma (up to 45%), bladder cancer (40%), and renal cell carcinoma (up to 25%) [75]. After diagnosis of bone metastases, median survival is highest in prostate cancer (up to 53 months), followed by thyroid cancer (48 months), breast cancer (up to 25 months), renal cell carcinoma (12 months), bladder cancer (up to 9 months), lung cancer (up to 7 months), and melanoma (6 months) [76]. Table 16.3 provides information on diagnostic imaging methods for the detection and evaluation of bone metastases.

There are three main types of bone metastases, which are classified according to the putative mechanism of interference with bone remodeling [77]. Osteolytic metastases are characterized by osteoclast-mediated destruction of normal bone and involvement of parathyroid hormone-related peptide [78]; osteolytic metastases comprise the majority of bone metastases in breast cancer and are present in multiple myeloma, renal cell carcinoma, melanoma, non-small cell lung cancer, non-Hodgkin's lymphoma, and thyroid cancer [76]. Osteoblastic (sclerotic) metastases are characterized by new bone deposition with transforming growth factor, bone morphogenic proteins, and endothelin-1 contributing to osteoblast generation [79]; osteoblastic metastases are present in prostate cancer, carcinoid, small cell lung cancer, Hodgkin's lymphoma, and medulloblastoma. Mixed bone metastases refer to the survivor having both osteolytic and osteoblastic lesions or if an individual metastasis is comprised of both components; mixed bone metastases can occur in breast cancer, gastrointestinal cancer, and squamous cell cancers.

Bone metastases confer significant morbidity and mortality in people with advanced cancer [80]. Bone pain, the most common type of pain from cancer, may have inflammatory (e.g., local release of cytokines and chemical mediators by the tumor cells) and mechanical (e.g., related to pressure or mass effect of tumor tissue within the bone) components [81]. The high prevalence and incidence of skeletal-related events (SREs), which include pathological fractures, hypercalcemia, and

spinal cord injury, contribute to poor performance status and decreased quality of life in cancer survivors [82]. Sudden onset back pain and neurological deficits are ominous for spinal cord compression, which is a medical emergency requiring magnetic resonance imaging, high-dose corticosteroid therapy, and urgent referral for surgical decompression and spinal stabilization [83].

External beam radiation therapy is the primary treatment modality for symptomatic bone metastases to reduce pain, achieve local tumor control, and improve quality of life [84]. Radionuclide therapy is the systemic use of radioisotopes for palliation of painful bone metastases; radiopharmaceuticals, such as strontium-89, are preferentially taken up at sites of bone formation, thus likely being most efficacious for osteoblastic metastases [85]. Pathological fractures occur in up to 30% of all cancer survivors, with the most common fracture site being proximal parts of the long bones, particularly the femur [86]. Movement-exacerbated pain is predictive for impending fracture, with primary internal stabilization followed by radiotherapy being the treatment of choice. Percutaneous vertebroplasty, wherein polymethylmethacrylate is injected into bone by percutaneously inserted needles under radiologic guidance, can alleviate pain from and stabilize pathological vertebral body fractures [87]. Locoregional techniques such as radiofrequency ablation [88], cryotherapy [89], photodynamic therapy [90], endovascular embolization [91], or chemical ablation [92] can facilitate tumor debulking. In select cancer survivors, surgery can correct and prevent further deformity through spine stabilization and nerve decompression [93].

The most common pharmacological agents for management of bone metastases are bisphosphonates, which inhibit osteoclastic bone resorption and are the primary treatment for hypercalcemia of malignancy [94]. Recent Cochrane reviews have shown that bisphosphonates appear to reduce bone pain, decrease the risk of developing SREs, and delay the median time to SRE in women with metastatic breast cancer that has spread to the bone [95]; reduce pathological vertebral fractures, SREs, and pain in multiple myeloma survivors [96]; and probably decrease SREs and disease progression in advanced prostate cancer survivors [97]. There is increasing evidence for the use of denosumab, a RANK-ligand inhibitor, in preventing SREs in multiple myeloma survivors [98]. Systemic opioids are the mainstay analgesic therapy for painful bony metastases [99]; corticosteroids, such as dexamethasone, are commonly prescribed as adjuvant therapy in survivors with limited life expectancy and painful bone metastases [100].

There is emerging evidence in support of exercise as a potential nonpharmacological intervention in the advanced cancer survivor with bone metastases. In a randomized controlled trial of a modular multimodal exercise program in 57 prostate cancer survivors with bone metastases, there were statistically significant improvements in self-reported physical function and objectively measured lower body muscle strength, with no skeletal complications or increased bone pain [101]. In a randomized controlled trial of guided isometric resistance training of the paravertebral muscles in 60 survivors with spinal bone metastases undergoing radiotherapy, there were statistically significant improvements in functional capacity and fatigue [102]. Larger, high-quality randomized controlled trials are needed

Table 16.4 Screening and exercise considerations for survivors with bone metastases

Screening considerations [76, 162]	Exercise testing and training considerations [102, 163–168]
Primary tumor type	Caution with/avoidance of passive ROM/stretching, ballistic movements
Type of lesion (lytic, blastic, mixed)	Consider limiting range of motion
Anatomical site of lesion	Consider single-plane movement patterns (i.e., avoid twisting/rotational movements)
Pain and other symptoms	Avoidance of resistance exercise in unstable or high-risk region
Presence of pain with weight-bearing of region	Consider weight-bearing restrictions or use of assistive devices to reduce weight-bearing or to provide support to region (e.g., lumbar support)
Extent of bone destruction – stability of lesion	Supported positions with consideration given to site of bone lesion
Medical treatment: surgical fixation, radiation therapy, pharmaceutical or other non-operative management	Physical and occupational therapy involvement: teach strategies for living safely with bone metastases

to establish the efficacy of exercise training in advanced cancer survivors with bone metastases. Table 16.4 includes considerations for screening and exercise training for the survivor with bone metastases.

Dyspnea

Dyspnea is a symptom experienced as "breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" and is the consequence of complex interactions between psychological, physiological, social, and environmental factors [103]. Multiple sensory inputs can contribute to the subjective experience of dyspnea, including (i) the sensations of work or effort, (ii) tightness which is specific to bronchoconstriction and stimulation of airway receptors, and (iii) air hunger/unsatisfied inspiration that arises from imbalances between inspiratory drive, efferent activation, and feedback from afferent receptors through the respiratory system [104]. A person with advanced cancer can experience both a chronic background level of continuous dyspnea and intermittent, acute episodes of breathlessness [105]. Dyspnea can only be perceived by the person experiencing it; therefore, self-report is a critical component of dyspnea assessment.

Dyspnea is present in up to 40% of patients at the time of diagnosis of advanced cancer [106], increases with disease progression [107], and occurs in up to 70% of patients in the last 6 weeks of life [108, 109]. Dyspnea is among the most feared symptom, as many report that they are unable to catch a breath or feel they are suffocating or drowning [110]. Dyspnea has been associated with fatigue, anxiety, and depression and can cause significant suffering in patients and their families [111,

112]. Dyspnea negatively impacts quality of life, including physical functioning and interfering with daily life activities [113].

The underlying etiology of dyspnea in people with advanced cancer is multifactorial. Pulmonary causes of dyspnea include airway obstruction, atelectasis, infection, interstitial lung disease, lymphangitic carcinomatosis, metastatic disease, pleural effusion, and pulmonary embolism [114]. Systemic causes of dyspnea include anemia, congestive heart failure, deconditioning, hypoxemia, pericardial effusion/pericarditis, pulmonary hypertension, muscle weakness, neuromuscular conditions, sepsis, and uremia [115]. Psychogenic causes of dyspnea include panic disorder, anxiety, and psychosocial distress [116]. Dyspnea may also be caused by adverse effects of anticancer treatment, including chemotherapy or radiotherapy-induced pneumonitis and fibrosis [117, 118].

Dyspnea management starts with comprehensive assessment of the symptom, its impact on the patient's experience, and treatment of any reversible etiologies [119]. Commonly used pharmacological agents for the management of dyspnea include systemic opioids, benzodiazepines, steroids, and oxygen therapy [120]. Non-pharmacological strategies for the management of dyspnea include anxiety reduction training, relaxation techniques, breathing exercises, environmental modification, and activity pacing and energy conservation [121]. Complex interventions that are administered by an interdisciplinary team, and which combine pulmonary rehabilitation with cognitive and behavioral management techniques, may be of benefit for advanced cancer patients with dyspnea [122, 123].

Exercise is one potential non-pharmacological strategy for the management of dyspnea in people with advanced cancer. In their 2019 Cochrane review of the effects of exercise training in adults with advanced lung cancer, Peddle-McIntyre et al. showed that upon completion of the intervention period, there was no significant difference in dyspnea between the intervention and control groups [25]; the evidence was graded as "low certainty" due to small sample sizes and significant risk of bias across the five studies [124–128]. Larger, high-quality randomized controlled trials are needed to establish efficacy of exercise training for dyspnea in patients with advanced lung cancer. Table 16.5 describes key considerations for screening, evaluation, as well as exercise testing and training.

Venous Thromboembolism

Venous thromboembolism (VTE) is a clinical syndrome characterized by blood clot formation in the veins and is comprised of two types, deep venous thrombosis (DVT) and pulmonary embolism (PE) [129]. DVT is the formation of blood clot in the body's large veins, most commonly in the lower limbs; PE results from dislodgement of the blood clot from the blood vessel where it formed and subsequently getting blocked in the lung [130]. Risk factors for VTE can be classified into two main categories: (i) idiopathic, primary, and unprovoked and (ii) secondary and

Table 16.5 Screening and exercise considerations for survivors with dyspnea

Screening considerations [103, 104, 113]	Exercise testing and training considerations [103, 104, 106, 169]
Dyspnea >4 on Borg 10-point	Consider resistance exercise to address muscle mass as starting point; introduce interval training within tolerance
Oxygen saturation <90%	Consider addition of inspiratory muscle retraining with respiratory training device
Respiration: note rate and quality: rapid, shallow, congested	Training and focus on breathing and control of breath during exercise: diaphragmatic, posterior/lateral thoracic breathing, pursed lip breathing
Severe dyspnea: respiration rate >14 breaths/minute at rest	Upright positioning: exercise in positions that allow optimal lung expansion and gas exchange (e.g., seated with back straight and legs wide apart)
Coughing, wheezing	Environment: cooler room temperature, open window, or use of fan on low speed to promote air flow
Symptoms associated with dyspnea: chest pain, pain with breathing, unable to get enough air, fear/panic	Teach escape positions to ease breathing (i.e., leaning forward in seated position with forearms braced on knees or table)
	Pacing of exercises: planned balance of rest with exercise

provoked [131]. Idiopathic, primary, and unprovoked risk factors include age >65 years, air pollution, cigarette smoking, hypertension, long-haul travel, metabolic syndrome, obesity, thrombophilia (factor V Leiden or prothrombin gene mutation), and no apparent cause. Secondary and provoked risk factors include cancer, acute medical illness (e.g., pneumonia, congestive heart failure), immobilization, oral contraceptives, postmenopausal hormonal replacement, surgery, pregnancy, and trauma.

VTE presentation can be asymptomatic. DVT can present with nonspecific symptoms like leg pain/ache/discomfort, sensation of warmth, tenderness, swelling, or discoloration, whereas PE can present with chest pain, dyspnea, palpitations, or sudden collapse [130]. Diagnosis of VTE begins with a clinical probability assessment, which incorporates clinical history (e.g., individual and familial presentation), physical examination (e.g., abnormalities in oxygen saturation, symptoms, or signs), and diagnostic imaging (e.g., abnormalities in chest radiography or electrocardiography) [132]. In survivors identified as having low clinical probability, VTE diagnosis can be ruled out by a blood D-dimer test; in those having intermediate or high clinical probability, compression ultrasonography or multidetection CT angiography is warranted. For the initial treatment, early maintenance, and long-term treatment of established VTE, low-molecular-weight heparins are the mainstay pharmacological therapy [133].

Cancer-associated VTE confers significant morbidity and mortality [134]. Cancer survivors are six times more likely to develop VTE than noncancer survivors, and survivors with cancer account for greater than 20% of all new VTE

diagnoses [135]. Incident VTE risk is higher in survivors with primary brain tumors and pancreatic, stomach, and lung cancers [136]. The use of systemic chemotherapy [137], indwelling catheters [138], and supportive therapies (e.g., red blood cell transfusions, platelet transfusions, and erythropoiesis-stimulating agents) [139] results in increased VTE risk. Increased tumor burden confers higher risk of VTE, and the presence of VTE is a poor prognostic sign [140]. After the cancer itself, VTE is the second highest cause of death in cancer survivors [140].

The role of exercise in people with cancer-associated VTE is unknown. The association between regular physical activity and incident VTE risk has not been established in healthy populations [141]. In a randomized controlled trial of adults who were receiving therapeutic anticoagulation after a first episode of unprovoked VTE, early initiation of exercise training resulted in improvements in physical activity and fitness, and symptoms related to postthrombotic syndrome, with no adverse events; people with cancer-associated VTE, however, were excluded [142]. In a retrospective study of 422 people postacute PE who participated in an inpatient rehabilitation program, there were no recurrent VTE or severe bleeds, and the individualized exercise program was deemed safe; however, none of the participants had cancer [143]. Further research is needed to determine the feasibility, safety, and efficacy of exercise in the prophylaxis of, and rehabilitation from, VTE in people with cancer.

Nausea

Nausea is an unpleasant, subjective experience which signals imminent vomiting, which may or may not result; vomiting, on the other hand, is an unpleasant symptom objectively experienced as forceful elimination of stomach contents by gastric cardia opening and sustained abdominal muscle contraction [144]. Between 6% and 68% of people with advanced cancer experience nausea [107], for which average intensity scores tend to plateau in the last 6 months of life [112]. In patients with advanced cancer who are admitted to hospice, 62% reported nausea and vomiting, whereas 34% reported isolated nausea and 4% reported isolated vomiting [145]. Vomiting was frequently unbearable (73%) for cancer patients within the last 6 months of life, when symptom intensity overall was low [146]. Nausea and vomiting contribute to dehydration, electrolyte abnormalities, weight loss, and the inability to take medications, and result in complications which interfere with treatment and social interaction [147]. In newly diagnosed cancer patients undergoing combined modality treatment, approximately two-thirds reported co-occurrence of nausea, vomiting, and appetite loss, which synergistically and negatively impacted overall quality of life (including physical functioning, fatigue, and overall health) and psychological distress [148]. Nausea is often undertreated in people with advanced cancer, with detrimental effects on quality of life [149].

Nausea and vomiting are centrally mediated by a diffuse, interconnecting neural network which results in the emetic reflex. Rather than a discrete vomiting center, the emetic complex involves groups of loosely organized neurons which are distributed between the prodromal-sign center (located in the reticular area dorsally adjacent to the semicompact part of the nucleus ambiguous) and the central pattern generator center (located dorsomedial to the retrofacial nucleus) [150]. Together, the prodromal-sign center (PSC) and central pattern generator center (CPGC) integrate afferent input from different areas throughout the brainstem and medulla: the vestibular nuclei and cerebellum, the higher central nervous system (CNS) centers, the nucleus tractus solitarius (NTS), and the chemoreceptor trigger zone/area postrema (CTZ/AP). Located in the floor of the fourth ventricle with no blood-brain barrier, the CTZ/AP contains chemosensitive nerve cell projections, which are directly exposed to noxious agents in the cerebrospinal fluid; drugs/toxins/metabolites in the systemic circulation are detected from the dense vascular network of fenestrated local capillaries therein. The major afferent neural pathway from the body to the central structures is the vagus nerve, with additional contributions from the splanchnic nerves, sympathetic ganglia, and glossopharyngeal nerve [144].

The underlying etiology of nausea and vomiting in people with advanced cancer is complex [151]. Cerebral cortical causes of nausea and vomiting include CNS or meninges tumors, increased intracranial pressure, anxiety or other conditioned responses, and uncontrolled pain [147]. Vestibular/middle ear causes of nausea and vomiting include vestibular disease, middle-ear infections, and motion sickness. CTZ/AP causes of nausea and vomiting include medications (e.g., opioid analgesics, chemotherapy, antibiotics, theophylline, digoxin), metabolic toxins (e.g., renal impairment, liver failure, tumor products), hyponatremia, and hypercalcemia. Gastrointestinal tract (GIT) causes of nausea and vomiting include irritation by medications (e.g., nonsteroidal anti-inflammatory medications, iron, alcohol, antibiotics), tumor infiltration, radiation therapy to the GIT, infection (e.g., candida esophagitis, colitis, history of radiation therapy), constipation/fecal impaction, incomplete tumor obstruction, bowel dysmotility, tube feedings, gag reflex from feeding tube, nasopharyngeal bleeding, and thick secretions [147].

Nausea and vomiting management is a mechanistic approach, which is based on identifying the likely etiology of nausea and vomiting, the putative pathway by which the cause triggers the emetic reflex, and the potentially involved neurotransmitters [152]. Non-pharmacological measures for managing nausea and vomiting include small, frequent meals consisting of food that the person desires, avoiding foods with unpleasant tastes or strong odors, and drinking frequent, small sips of fluid [144]. Treatment of reversible causes of nausea and vomiting includes whole-brain radiotherapy for brain metastases, antibiotics for middle-ear infections, antifungal therapy for gastrointestinal tract infections, reducing tube feeding volumes, laxatives and manual disimpaction for constipation, and hydration and pamidronate for hypercalcemia. Commonly used pharmacological agents for the management of nausea and vomiting in people with advanced cancer include dexamethasone [153], levomepromazine [154], haloperidol [155], olanzapine [156], and metoclopramide [157]. In people with advanced cancer not receiving antineoplastic therapy,

pharmacological agents associated with a statistically significant decrease in nausea/vomiting were olanzapine, laxatives, corticosteroids, domperidone, and metoclopramide [158].

There is emerging evidence regarding exercise as one potential non-pharmacological strategy for the management of nausea and vomiting in advanced cancer patients. In a randomized controlled trial of a combined nutrition and exercise program in 58 survivors with metastatic or locally advanced gastrointestinal and lung tumors, nausea and vomiting increased less in survivors of the intervention group than in survivors of the control group ($p < 0.01$) [159]. Larger, high-quality randomized controlled trials are needed to establish the efficacy of exercise training for nausea and vomiting in people with advanced cancer.

Summary

This chapter has described the background information and practical aspects related to exercise screening and delivery, including special considerations for the survivor with advanced, metastatic, and terminal cancer. The challenges facing the exercise specialist are complex and involve identifying symptoms, functional impairments, and co-pathologies that may impact exercise risk and tolerance and adapting exercise programming to allow the patient to participate safely, comfortably, and effectively.

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Part IV
Behavior, Logistics, and Policy

Chapter 17
Cancer Survivors Becoming and Staying Physically Active: Challenges of Behavior Change

Bernardine M. Pinto, Madison M. Kindred, and Chloe Grimmett

Introduction

Physical activity (PA) guidelines for cancer survivors have been developed in several countries including the United States, Canada, and Australia [1–4] among others. However, only 20% of survivors in the United States reported exercising (aerobic and strength training) at the recommended levels [5]. Much work remains to be done to determine how best to implement the PA guidelines/recommendations. The promotion of PA along the cancer diagnosis and survivorship continuum requires behavior change. Although a cancer diagnosis may present a "teachable moment" (or "phase") [6] when survivors may be more receptive to advice and assistance in making lifestyle changes including becoming physically active, the window(s) of opportunity requires behavior change not only from the individual survivor as is commonly assumed but also from the healthcare providers (HCPs), family, peers, and community. In this chapter, we will attend to the behavior change required not only of the survivor but also from those whose behavior impacts the individual survivor. We will review the application of theories and techniques of behavior change that have been used to promote PA adoption and maintenance. We will then proceed to describing the challenges of behavior change at the survivor level, followed by family, friends, and peers, and at the level of the HCPs. There is scope for using new technology to overcome barriers to change at each of these levels and expand the reach of PA interventions: the potential uses are described.

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Theories, Constructs, and Behavioral Change Techniques

Behavior change at the individual level has been the focus of many PA interventions offered to cancer survivors (see reviews [7–9]). Several theoretical approaches have been used in some of these interventions, notably, theory of planned behavior, transtheoretical model, social cognitive theory, cognitive behavioral theory, and theory of self-determination among others (see description of theories [10–12]). Key constructs from the theory of planned behavior [13] include attitudes toward PA, subjective norms, perceived behavioral control, and behavioral intentions. The relationship of these constructs to behavioral intention and PA has been examined in numerous cross-sectional studies [14, 15] and has been applied to interventions [16, 17]. From social cognitive theory (SCT) [18], key constructs that have been examined are knowledge of health risks and benefits, perceived self-efficacy, outcomes expectations (expected cons and benefits), health goals and intentions to engage in the behavior, perceived facilitators, social support, and barriers to making changes. Techniques based on these constructs have been implemented to varying degrees in interventions. Motivational readiness for change, decisional balance, and the processes of change from the transtheoretical model (TTM) [19] have guided some interventions [20–22]. The application of these approaches in efforts to promote exercise adoption has led to the identification of variables such as self-efficacy for behavior change, intention to change behavior, and behavioral processes of change as key to encouraging sedentary survivors to become physically active.

In addition to behavior change theories, motivational interviewing as a technique has been used to promote lifestyle change among cancer survivors (including increasing PA), psychosocial support, and the self-management of cancer-related symptoms [23]. This patient-centered approach uses open-ended discussions and reflective listening to encourage patients to explore their own goals and motivations for change [24]. Six studies that used motivational interviewing for PA promotion (three were randomized controlled trials [RCTs] and three cohort studies) showed small-to-moderate effects on PA, but the interventions were associated with high dropout rate when offered concurrently with chemotherapy [23].

Despite the growing number of PA interventions for cancer survivors, it is premature to reach conclusions about which theory/theories and theoretical constructs are more effective in producing significant improvements in PA participation. Sparsely described interventions, variations in the extent to which constructs are implemented, lack of information on mechanisms of effects, and modest effects of the interventions among others make it challenging to endorse one or more theories.

Behavior Change Techniques Behavioral scientists have begun to recognize that to better understand how interventions are exerting their effects, it may be more appropriate to scrutinize their individual intervention components, irrespective of any attributed theoretical underpinning. This gap can be addressed if researchers use a standard system to describe the techniques used in their interventions. To facilitate accurate and consistent reporting on techniques, Michie and colleagues developed

the Behavior Change Technique Taxonomy v1 [25]. This provides a standardized method of reporting intervention components (known as behavior change techniques [BCTs]). The taxonomy includes 93 individual BCTs defined as "observable, replicable and irreducible components of an intervention designed to alter or redirect causal processes that regulate behavior."

In a review of 18 RCTs using SCT (alone or with TTM; 10 of which focused on exercise, 1 on diet, and 7 addressed exercise plus diet), Stacey and colleagues [26] found that SCT-based trials produced small-to-moderate effects on PA at 12 weeks (effect size of 0.33). For this review, the authors [26] used an early version of the taxonomy, the CALO-RE taxonomy [27], and coded BCTs that map to the constructs of SCT. Goal-setting and self-monitoring were commonly included techniques, but their effectiveness was not described. Increases in self-efficacy were associated with increases in PA in three trials with moderator analyses showing that those with higher self-efficacy increased their PA faster than those with lower self-efficacy. The most common tool to increase self-efficacy was to provide survivors a pedometer or a PA log. Social support was the most common outcome expectancy targeted. Mediation analyses identified that improvements in barrier interference and barrier self-efficacy mediated 39% and 19% of intervention effects on PA maintenance, 3 months after the intervention ended.

A meta-analyses of 14 RCTs among breast cancer survivors (2005–2013) by Bluethmann and colleagues [28] showed that home-based settings and walking were common elements in the trials that produced a standardized mean difference of 0.47 for moderate-intensity PA. The authors found that larger effects were produced by highly structured programs with more intensive supervision (e.g., in person, standardized mean difference of 0.69), but interventions delivered by phone or mail that required less resources were also effective (pooled effect size = −0.56). Key components of the programs included individual counseling or coaching and workshops or peer support groups for the participants. Although the authors did not use Michie's taxonomy of BCTs to identify active ingredients of the interventions, self-monitoring was also found to be associated with effective PA outcomes. Interestingly, studies with the largest sample size or the longest exposure to the intervention were not more effective in producing behavior change.

In a subsequent review, Bluethmann et al. [28] applied Michie and Prestwich [29] framework on behavior theory coding and selected eight items to assess the extent to which theory was applied in the 14 RCTs. They found that the majority of the trials used the TTM[19] ($n = 6$) and SCT[18] ($n = 4$). Trials that used the theory more intensively (fulfilled six or more items) had the largest overall effect size for behavior change (5 studies, Hedges' $g = 0.76$, standardized mean difference). The techniques used were stage of readiness matching, goal setting, social support, monitoring, feedback, modeling, and problem solving. In another review of behavioral interventions for breast cancer survivors [30], where aerobic PA was the targeted outcome, 8 of the 10 RCTs produce significant effects. Although Michie's taxonomy [25] was not used in this review, the trials used self-monitoring, goal setting, getting social support, and positive reinforcement.

More recent reviews have used Michie's taxonomy in evaluating the active components of interventions and their association to PA outcomes. An update of a 2013 Cochrane review which included 23 studies (total of 1372 participants treated for breast, prostate, colorectal and lung cancer) showed that BCTs associated with trials that achieved adherence of 75% or more to PA guidelines during the trials were characterized by goal setting, setting graded tasks, and instruction of how to perform behavior [31]. Another meta-analyses of 30 RCTs of interventions that did not require professional guidance, specific facilities, or equipment identified the effect size associated with various BCTs [32]. Overall effect sizes of the interventions were small ($g = 0.316$ for self-reported PA and $g = 0.182$ for objectively recorded PA). They found that providing prompts, reducing prompts (as in reducing frequency/intensity of phone calls), setting graded tasks (e.g., increasing frequency/duration/intensity of PA), and use of nonspecific rewards and social reward were associated with larger effects, while information about health consequences and information about emotional consequence and social comparison (with others' PA, or PA goals vs. actual PA) were related to smaller effects.

Other quantitative reviews of RCTs (conducted largely among breast cancer survivors) have not only highlighted the use of BCTs but also pointed to the importance of variation in the methods of *implementing* them. Those that were delivered individually person-to-person and those with interactive elements (e.g., audit and feedback) tailored to the individual needs of patients were most effective in improving PA behavior [33].

In preparation for the International, Multidisciplinary Roundtable on Exercise and Cancer Prevention and Control (2018), experts distributed an online survey of currently available exercise and rehabilitation programs worldwide. Survey respondents were recruited via email to opinion leaders and organizations offering established programs, professional organizations such as Livestrong, American College of Sports Medicine, Society of Behavioral Medicine, and snowball sampling [34]. More than 50% of the 257 programs identified in the survey endorsed using individual techniques such as goal setting, self-monitoring, guidance on overcoming barriers, regular feedback (e.g., on fitness, PA), and getting support from family and friends. These data suggest that many of the BCTs techniques identified in the scientific literature are reported to be used (likely to varying degrees and by various tools) by community-based and medically supervised exercise programs offered to cancer survivors.

Maintaining PA: Behavior Change Techniques The majority of behavioral science evidence in the context of PA promotion in cancer populations has focused on the adoption of PA. Much less attention has been paid to the effectiveness on maintenance of PA behavior with numerous reviews describing a lack of evidence as to how to support sustained improvements in behavior [9, 26, 28]. Grimmett et al. [35] presented the first synthesis of long-term PA following interventions in cancer populations, including all RCTs with an assessment of PA behavior a minimum of 3 months after intervention completion. The authors coded all BCTs present in these studies and examined their association with effectiveness. The BCTs of goal

setting, self-monitoring, instruction on how to perform a behavior, and problem solving were common across all studies irrespective of effectiveness. BCTs that were exclusive to studies achieving significant behavior change at follow-up included graded tasks, social support, and action planning, suggesting that these additional components may support maintenance of behavior. There are some similarities with a review of PA interventions in healthy inactive adults, which also found action planning and graded tasks to be associated with maintenance of behavior 6 months or more after intervention completion, in addition to instruction on how to perform the behavior, prompts/cues, behavior practice/rehearsal, and self-reward [36].

Limitations of the Behavior Change Literature

The behavior change literature offers some suggestion of intervention components that may increase the effectiveness of future PA promotion programs in people affected by cancer. However, it also has important limitations. First, although theories and techniques of behavior change have been applied to aerobic exercise interventions, the challenges of behavior change for resistance training have merited scant attention. Second, it is often the case that more than one theory has been used to guide the intervention, so it is difficult to identify the unique contributions of the individual theory. As discussed in previous work [10], there have been little direct comparison of interventions based on different theories, and hence, it is not possible to unequivocally recommend one or more theories.

Third, a majority of the theory-based PA interventions have been offered to white women, with early-stage diseases living in medium-to-large metropolitan areas, used self-reported exercise, and many did not explore the maintenance of behavior change beyond 6 months of intervention completion [26, 28]. PA interventions for cancer populations also tend to include individuals with good physical function. In a large multimodal lifestyle intervention of older long-term cancer survivors, those reporting low physical function at the start of the study struggled to increase their PA, yet the program was effective among the rest of the cohort [37]. This suggests that different approaches may be required to support individuals with functional limitations. It is also important to note that participants will have chosen to take part in these interventions and thus are already motivated to become more active. Indeed, participants in existing trials were typically already engaging in at least some PA on entry to the study. As such, alternative strategies may be necessary to promote behavior change among those people affected by cancer who are inactive and/or less engaged with the notion of change.

Fourth, there is a call for researchers to consistently apply theory during intervention development, identify the theory-based determinants of behavior, target the determinants with the appropriate theoretical change methods, implement, and finally evaluate the effects on PA. The use of the BCT taxonomy to identify effective components of interventions is an important step in reliably synthesizing the

available evidence; however, not all reviews have used Michie's taxonomy [25], thereby making it difficult to reach conclusions about the most effective BCTs. Incomplete reporting of intervention content often makes it difficult to ascertain which BCTs were included and/or whether implementation strategies were implemented effectively.

Contextual Approach to Behavior Change

"Behavioral science…especially within the U.S. has focused primarily in *individual* health-related behaviors without due consideration of the social context in which health behaviors occur" [38]. Hence, changing behaviors among patient populations need to move beyond the focus of the individual survivor. The Institute of Medicine (2001) has proposed that behavior change be conceptualized as a multilevel problem [39], and the approach to cancer care is shifting from a reductionist approach (e.g., single programs, isolated stops in care) [40] to contextual behavior change. Multilevel approaches such as those cogently described by Taplin and colleagues [40] delineate an "onion" approach, where the patient (the "core") is embedded in a support environment (family, friends, peers, etc.), the healthcare environment, the PA setting (clinic/community/hybrid/other) (the inner layers), and health policy at the local, regional, and national levels (the outer layers of the onion). This approach can be adapted for PA promotion for cancer populations and takes into consideration broader determinants of behavior including the context and delivery characteristics that may impact the adoption and maintenance of PA (Fig. 17.1).

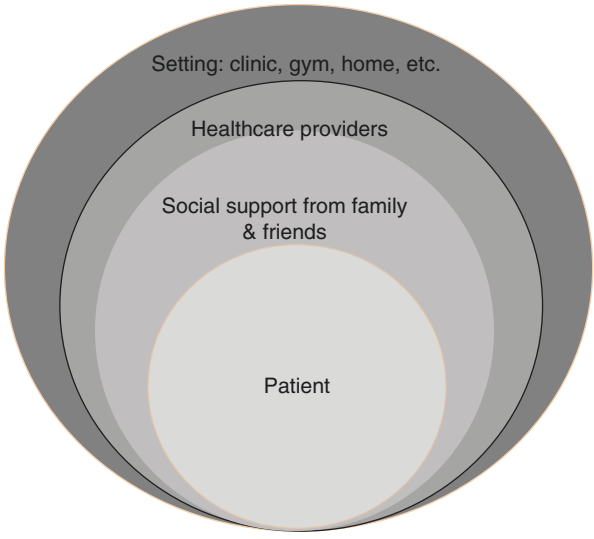

Fig. 17.1 Promoting physical activity among cancer survivors: a multilevel approach

Behavior Change: Overcoming Barriers at the Survivor Level

Research has indicated that among cancer survivors, PA can be tolerated both during and after cancer treatment [8]. A large body of evidence surrounds the benefits of PA among cancer survivors [41]. Despite the known benefits of PA, cancer survivors [5, 42, 43] are not meeting the recommendation of 150 minutes of moderate-intensity activity per week [1]. There are a variety of patient-level barriers related to inactive or low PA levels, such as lack of advice from an oncologist [44], disease and treatment side effects (e.g., joint stiffness, pain, weakness, and fatigue [45–48]), and/or overall lack of interest in participating. Some of these barriers are described below:

Cancer-Related Barriers

Physical exertion may be daunting to a survivor who has recently completed treatment. The treatments that patients receive can exact a physical and emotional toll that could interfere with activity. Cancer-related fatigue, which can begin during active treatment and be long-lasting, is often cited as a barrier [49–52]. In addition, surgical restrictions can limit the types of activities a patient is able to successfully perform. For example, pains and aches, neuropathy, and joint stiffness from treatment have been cited as barriers to activity [53]. Adjuvant treatments (chemotherapy and/or radiation) may adversely affect the immune system, and hence, patients are usually advised not to exercise at a high intensity during and toward the end of active treatment [8, 54]. In all cases, survivors will need to rely on guidance and advice of their HCPs to ensure that they are completing activities that are safe and feasible given any treatment-related restrictions.

Noncancer-Related Barriers

In addition to their cancer diagnosis and treatment, survivors may also have comorbidities or health conditions which can lead to low levels of PA [52, 55]. Older cancer survivors who are the majority of the survivor population have to cope with the effects of the aging process (e.g., arthritis), which can lead to an inactive lifestyle [52, 53, 55]. Lack of PA can also lead to increased body weight that in turn can impede the individual exercising at moderate or higher intensity PA. Psychologically, survivors may have a fear of causing injury or falling during an exercise session. Furthermore, lack of motivation is a barrier among both cancer survivors and healthy adults [56, 57]. Lastly, previous history of PA may affect a survivor's willingness to become physically active: in a systematic review, survivors who were active prior to diagnosis were more motivated to begin exercising following diagnosis compared to those who were not active [55].

A cancer survivor with additional health concerns (e.g., cardiovascular disease, diabetes, obesity) should not be hindered from adopting PA. For those survivors who are just starting to become active, participating in activities at a light intensity (e.g., walking at a casual pace and gardening) may be a reasonable and feasible place to begin. Achievement of light-intensity PA goals can enhance self-efficacy for PA, and such activities have been shown to improve quality of life [58] and physical functioning [59] among cancer survivors. It is also possible that light-intensity PA can serve as a gateway to activities of higher intensity in keeping with PA guidelines for cancer survivors.

Survivor Preferences for Activity

Preferences for PA programs are varied and can be dependent on the venue (e.g., travel distance, ease of parking), class schedule, presence of supervision, and type of exercise. A majority of cancer survivors prefer to receive exercise counseling [60]. On-site or clinic-based programs offer the advantages of in-person supervision, an encouraging and safe environment [55], and opportunities for social interaction. A majority of survivors prefer to be instructed by an exercise specialist who is affiliated with a cancer center [60], to reduce their fear and to provide them proper guidance. On-site programs also offer personalized instruction and allow for proper exercise demonstration (e.g., stretching and/or resistance exercises appropriate for each survivor) [60]. Alternatively, on-site programs are costly and require transportation and an appropriately trained instructor to lead the program. Delivery of PA programs within the home/neighborhood can lessen the burden of travel and allow for flexibility of schedules, and hence, it is more convenient [55]. Previous research has shown that older adults prefer home-based programs or those in which the individual exercises alone [60, 61]. However, home-based programs require self-motivation [62] and may be more effective for an individual with a previous history of regular PA.

In addition to program location, preference for activity type should be considered. Walking is the most preferred form of PA among survivors [55]. Other preferences included exercising at a moderate intensity (compared to high intensity) and reducing boredom by having the ability to participate in a variety of programs [55]. Preferences for a type of PA may also be influenced by the survivor's culture and geographic location. For example, Nordic walking has been offered to breast cancer survivors in the Netherlands [63], while dragon boat racing is a common type of PA among survivors located near a body of water [64]. Survivors report that while their HCPs may encourage PA activity, there is a need for further education to develop an individualized plan for PA participation [52, 55]. Qualitative data reveal that survivors want programs that are individualized and will yield benefits specific and meaningful to them and focused on symptom management (e.g., reduced fatigue) and functional independence [55].

Social Support for PA: Behavior Change Among Family, Friends, and Peers

The Cancer Care Continuum extends from primary prevention to end-of-life care [65], and as a patient moves through the Continuum, there are a variety of interfaces that can occur to support the adoption and maintenance of a physically active lifestyle. The context of behavior change encompasses social support from family, friends, and peers. Adult cancer survivors perceive social support for PA as a way to provide them companionship (shared experience), motivation (encouragement to participate in PA), and health promotion (associated benefits such as reduced stress) [55, 66]. Commonly defined as assistance to perform a specific behavior, social support has been identified as a gateway to increasing PA levels among adults with chronic disease(s) [67]. The individual(s) offering support may actively participate by walking with a survivor [68, 69] or may be a sounding board to discuss the benefits and risks of activity with a survivor [52]. Regardless of who provides the support or how the encouragement is delivered, cancer survivors' PA is positively influenced by those around them [70].

Peer support has traditionally been provided face-to-face, where members of a support group meet, discuss, and deliver information. While this method of delivery may be comforting and offer a welcoming environment for socializing, it is not practical for those survivors who work full-time, are unable to drive, and/or live in a rural community [71]. Fortunately, with the improvements in internet connectivity and web-based programs, survivors can receive support from their home. There is evidence that peers can provide effective individualized guidance to breast cancer survivors that results in increased PA [72, 73]. With the development of technology, survivors can now access support through online resources, discussion boards, and social media outlets. For example, patients can register and participate in a variety of discussion boards [74], such as breastcancer.org [75] or the American Cancer Society's Cancer Survivors Network [76]. Social media platforms such as Facebook have been used to increase PA [77] and other health-related decisions [78] among young adult cancer survivors.

Healthcare Context for Helping Survivors to Become Physically Active

There have been efforts to train HCPs to provide exercise counseling similar to effective counseling for smoking cessation (e.g., ask, advise, agree, assist, and arrange for follow-up) [79] in patient populations and healthy adults in the primary-care context [80, 81]. In 2007, the American College of Sports Medicine and the American Medical Association launched the *Exercise is Medicine* Global Health Initiative to make assessment of PA and exercise prescription a standard part of

disease prevention and treatment. This approach to viewing exercise behavior as another vital sign in healthcare can serve as a starting point for advising patients to become and/or stay physically active and providing referrals. In the cancer care setting, more recent work suggests that an oncologist's recommendation to exercise alone did not increase survivor's exercise [22, 82], but their referrals to exercise programs can be effective [83].

In an ideal scenario in an oncology setting, the first step is to *ask* survivors about their PA during medical visits. Assessment of PA using self-report such as the two-question format of Exercise Vital Sign [84] or wearable devices (e.g., activity trackers, accelerometers) can facilitate counseling that is tailored to the patient. The next step is to provide tailored *advice* to the survivor about the specific benefits that regular PA can provide – advice tailored to the survivor's specific symptoms (immediate, long-term, and late effects of cancer treatment) – as well to other health concerns (e.g., weight gain, diabetes management). When the survivor agrees that exercise might help in the management of cancer-specific symptoms (e.g., fatigue, poor physical functioning), the provider can *assist* them to explore resources to become active by providing *referrals* to specialty services (e.g., PT, OT) if necessary, to on-site supervised programs in either a medical setting or a community-based program (to access a world-wide registry of programs go to https://www.exerciseismedicine.org/movethruca) or other distance-based programs (m-health, telephone-based, print materials, etc.). It should be noted that it is not only the healthcare team in the oncology setting that can help triage survivors to the appropriate exercise program but also the primary care providers to whom cancer survivors transition for long-term care. The providers' willingness to bring up the topic in the encounter, their expressed confidence that regular PA can help in recovery, referral to appropriate and effective programs, and *following up* with continued exploration of progress (or lack thereof) at subsequent visits can reinforce the survivor's effort to become and stay physically active. By repeating "*Ask, Advise, and Refer*" at subsequent visits particularly among survivors who have not acted on the provider's earlier advice to become active will convey to the survivor that their HCP deems PA to be important to their functioning and recovery. Likewise, family members, friends, or caregivers who are aware of the providers' attention to the survivor's PA can also support and encourage the survivor to become physically active.

The impact and role of the HCP should not be underestimated: the survey conducted for the Roundtable on Exercise and Cancer Prevention and Control (2018) mentioned earlier in this chapter showed that the majority of programs (medically supervised and community-based) do require physician prior approval for survivors' participation (84% of respondents stated that referrals came from oncologists). As discussed in another chapter, more pragmatic implementation approaches for PA promotion are needed to deliver sustainable models that can be effectively integrated into the various forms of healthcare delivery in the United States. Some of the barriers to implementation include the lack of smooth, appropriate, and effective triage of survivors into medically supervised PA programs and/or community-based programs, care coordination and difficulties in following the progress of a

referred survivor, and fragmentation of care. These barriers have long been recognized as contributors to survivors getting lost in transition between various providers/healthcare professionals and services [85]. Financial barriers, payment models, workflow barriers, and providers' knowledge, motivation, and readiness to promote PA underlie the need for change at many levels beyond that of the individual survivor and extend to local, regional, and national healthcare policy. Nonetheless, these issues are not unique to exercise promotion in oncology. Recognizing the need to link cancer survivors to PA programs, researchers and practitioners on expert panels have proposed potential implementation approaches or pathways to address this gap [34, 86]. Exemplars of effective implementation approaches that addressed some barriers can be found both in PA promotion in the general healthcare setting (see Position Statement of the American Heart Association [80]) and in oncology care [87].

Use of Newer Technologies for PA Promotion

PA interventions for cancer survivors have been delivered via telephone, print, and the web with varying degrees of success [88–90]. While traditional face-to-face interventions such as on-site supervised programs are often effective, they will have limited impact if they cannot be used by large groups. There is scope for using new technology-based interventions that can extend the reach, adoption, implementation, and impact of PA interventions and offer the potential for providing less costly, effective programs for the large population of cancer survivors. Distance-based programs (print, telephone, web, m-health, etc.) can reach more survivors and can be less burdensome for survivors who experience treatment-related effects and long-term and late effects. However, the lower level of supervision may produce smaller effects on outcomes such as fitness and functioning [91].

The rapidly changing landscape of m-health applications and the use of wearables (pedometers, accelerometers) have led to a proliferation of apps for PA, fitness goals, and the like. These technologies avoid many of the problems associated with survivors' self-reported data; however, their penetration into oncology has been limited. In the general healthcare field, PA trackers can be used among a variety of patients; some drawbacks are that pedometer devices are not sensitive to some types of activity (e.g., cycling, swimming, resistance training); other trackers such as Fitbit™ (Fitbit Inc., San Francisco, CA) and ActivPAL TM (PAL Technologies Ltd., Glasgow, UK) allow for real-time monitoring, are relatively inexpensive, and allow data to be downloaded wirelessly onto a computer or mobile phone, and the data can be stored and analyzed on-line. Step tracking may be a stronger predictor of changes in PA during cancer treatments, and these objective data may be better indicators of changes in symptoms and functioning than clinician evaluations of functioning (performance status) or patient-reported symptoms [92, 93]. Obtaining data from activity trackers may be particularly useful for clinicians working with survivors in rural areas who would otherwise have to incur

expenses and the burden of travel to clinic appointments. Some wearables obtain additional data on sedentary time, moderate-to-vigorous PA, pulse oximetry, heart rate, and sleep time, which may also be useful to the healthcare team. A review of 41 trials where pedometers or accelerometers were worn by patients receiving cancer treatments and those in the posttreatment phase (a majority treated for breast cancer) showed that survivors typically take 4660–11,000 steps/day and those undergoing treatment take 2885–8300 steps/day [94]. Assessments of PA during treatment using such devices that can be worn for extended time periods may be a useful index of changes in patients' function and performance and provide longitudinal data to clinicians.

Beyond assessment of PA, wearable devices can be used by HCPs to motivate survivors to become and/or stay physically active, encourage and reinforce their efforts, and refer survivors to more specialized programs, if necessary (e.g., physical therapy) or community-based exercise programs. A review of 12 RCTs that used digital activity trackers (eight trials used pedometers) among 1450 cancer survivors showed significant improvements in survivors' step counts, PA levels, and quality of life but did not impact biomarkers [95]. The uptake of such devices may vary considerably: the devices do need to be charged periodically and their use may be limited among older cancer survivors/others with limited access to the internet or wireless technology (including some rural areas). The sensitivity of the devices among frail patients who move cautiously and those with limited capacity to perform activities of daily living may not be ideal. Purchase and use of wearables for survivors will involve not only the financial costs of the devices but also require attention to many other challenges: patient privacy, costs involve with gathering and processing data, customization to the healthcare setting (e.g., outpatient clinic vs. hospital, rural vs. urban), data summarization into a format that is easily understood and useful to the clinician (i.e., "more" is not necessarily "better"), integration with electronic health records and/or uploads into patient portals, integration with the staff workflow, and clarification of roles and responsibilities of the members of the healthcare team are other costs involved with implementation of these newer technologies.

Social media platforms and the use of social networks also provide opportunities for the integration of behavior change interventions. Survivors on support group networks can assist each other not only in coping with symptoms and sequelae of treatments, advice on talking with HCPs, and the like but they can be used to encourage and support lifestyle changes such as PA. For example, theoretically driven constructs and BCTs (skill building, goal setting, feedback, discussion prompts for social support) were used in a Facebook-based PA intervention for young adult cancer survivors [77]. Similar interventions may appeal to survivors who are accustomed to using these platforms and have the potential of reaching large groups of survivors. There are thousands of lifestyle-oriented applications available for smartphones (Apple, Android, etc.) or tablets for the general population. Less is known about the use and effectiveness for cancer survivors (e.g., Quintiliani et al. [96]) or indeed about the use of theory-based apps. Investigators have begun to explore the use of commercially available apps (that may have greater

generalizability), as well as those developed by healthcare experts to track various parameters of PA and provide feedback to the individual survivor [97, 98]. The data collected by these new technologies could be shared with healthcare professionals (oncologists, nurses, physical therapists, occupational therapists, etc.) for feedback and additional personalized guidance at appointments either in-person or via tele-health.

Future Directions

The issue of PA guidelines for cancer survivors in several countries has facilitated encouraging cancer survivors to become physically active. However, the uptake of these guidelines has been far from optimal. A multitude of interventions (theory based and atheoretical) have been offered to cancer patients at various points in the Cancer Care continuum, and many of these focused on the individual survivor and have achieved modest success. We urge oncology researchers and exercise promotion experts to attend to contextual factors as well as individual–/survivor-level characteristics. More specifically, we recommend that developers of PA interventions (researchers and community-based program developers):

- Use Michie's behavior change taxonomy [25] approach to code their programs so that in time, behavioral scientists can begin to answer questions such as what intervention(s) works, for whom, in what setting, and for which outcome?
- Describe the extent to which theories of behavior change have been used and how the theories have been implemented and evaluated in their programs.
- Recognize the need to go beyond individual-level theories and consider multilevel approaches/theories to support survivors' adoption and maintenance of PA.
- When describing interventions, use guidelines such as TIDierR (https://www.bmj.com/content/348/bmj.g1687) to capture important elements of context and implementation and to facilitate replicability.
- Facilitate the HCP role in ensuring that survivors are encouraged to become physically active.
- Use technology to enhance the reach of interventions while attending to the key BCTs.
- Use social support networks to encourage survivors adopting PA and sustaining a physically active lifestyle.

Continuing to identify key constructs, the corresponding BCTs, evaluating the effects on the outcome(s) of interest and mechanisms of the effects will assist in developing interventions that are parsimonious (with associated advantages of reduced expense and less burden on the survivor). Identifying the essential constructs and techniques ("active" ingredients) is even more important when one considers the need to develop cost-effective programs in a healthcare landscape of limited resources. Taking a "stepped care" approach, using more labor and time-intensive components such as individual counseling only for those who need more

assistance, could help address this need. Finally, new approaches to intervention design (e.g., Just-in-Time Adaptive Interventions, Multiphasic Optimization Strategy, Sequential, Multiple Assignment Randomized trials [99–101]) may allow researchers and program developers to identify the most effective components of programs before assembling a multicomponent intervention.

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Chapter 18
Making Exercise Standard in Cancer Care

Karen Basen-Engquist and Nathan H. Parker

Introduction

Increasing evidence suggests that exercise improves prognosis and survival after cancer and that physical activity interventions can improve physical functioning and quality of life in cancer survivorship. Observational studies indicate that insufficient physical activity is associated with adverse disease-related outcomes [1–10], including risk of recurrence, secondary malignancies, cancer-related death, and overall mortality [11–15]. Furthermore, physical inactivity is an established risk factor for cardiovascular disease [16], which is a significant cause of mortality for many cancer survivors [17–20]. Physical inactivity is also a risk factor for diabetes mellitus, which may increase the risk for additional cancer events [21]. Evidence for the effects of physical activity on cancer prognosis are difficult to test in randomized controlled trials using survival endpoints, because detection of mortality differences requires extensive follow-up time. However, there is substantial evidence from randomized trials supporting the use of physical activity interventions to improve quality of life – including physical functioning and fitness outcomes – and reduce symptom burden [22–28].

With increasing evidence demonstrating physical activity benefits for cancer survivors, the American Cancer Society (ACS) has published physical activity guidelines for cancer survivors [29], as have other organizations including the American College of Sports Medicine (ACSM) and the National Comprehensive Cancer Network [30–32]. For cancer prevention (primary and secondary) as well as many cancer health-related outcomes, the guidelines are generally consistent with those provided to the general population for cancer prevention and other health benefits: (1) avoid inactivity and return to normal daily activities as soon as possible after

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diagnosis; (2) aim to exercise at least 150 min per week; and (3) include strength training exercises at least 2 days per week. With the publication of the new ACSM guidelines in 2019, there are more specific exercise prescriptions for a group of eight cancer health-related outcomes for which there was sufficient evidence. Those specific guidelines, for fatigue, depression, anxiety, pain, lymphedema, sleep, bone health, quality of life, and function, can generally be summarized as 30 min of aerobic exercise thrice weekly and resistance exercise twice weekly [32]. Cancer survivors generally have limited awareness of these exercise guidelines, and only a few consistently achieved the recommended levels of aerobic or strengthening exercise goals [33–39]. Clinicians in both oncology and primary care have limited knowledge of physical activity guidelines and are rarely prepared for effective exercise counseling with their patients [40–42]. The importance and safety of exercise may be confusing to both survivors and healthcare providers due to lack of relevant education and misinformation on the Internet or in the community. Further, effective programs and services to help survivors maintain or increase physical activity are not widely available in survivorship care settings or the community across the USA. In this chapter, comprehensive and systematic support to increase physical activity in cancer care is encouraged. We envision a future cancer care environment in which appropriate and effective exercise programs are available to all survivors, from diagnosis onward, in order to optimize health. In this chapter, we use the phrase "cancer survivor," in alignment with the National Cancer Institute definition "of any person who has received a cancer diagnosis from time of diagnosis through end of life" [43].

This chapter describes three steps necessary for translating existing research regarding the benefits of exercise among cancer survivors into evidence-based and actionable practices [44, 45]. With goals of increasing the availability, accessibility, and uptake of programs to promote exercise and long-term adherence to guidelines among cancer survivors, we propose the following action areas:

1. Expand the availability of various evidence-based physical activity programs for survivors.
2. Provide patient-centered screening and referral of cancer survivors to exercise services/programs.
3. Expand dissemination and implementation research to test service delivery models for evidence-based exercise interventions.

Expand the Availability of Evidence-Based Physical Activity Programs for Survivors to Provide a Diversity of Formats and Delivery Channels

Cancer survivors have a range of needs, interests, and goals with regard to physical activity, and programs must reflect this diversity. Exercise programming can be supervised or unsupervised and offered in a clinical setting or the community; each

format involves different, yet important, roles for professionals. Some survivors may be able to exercise independently; others may face barriers that make unsupervised exercise challenging or even unsafe. These survivors therefore need to engage in structured cancer rehabilitation or cancer-specific supervised exercise programs before proceeding with home- or community-based programs [46]. Due to differences in resources, logistics, and personal preferences, survivors may be inclined to exercise in programs offered in a range of settings and structures: cancer treatment centers and community-based, or home-based, self-led programs. Survivors also differ in their motivations for exercise. Some seek lifestyle change to help prevent future health problems, while others need to remediate activity limitations or functional impairments through medical rehabilitation. Mobile health intervention strategies such as wearables and mobile phone applications may be useful across the range of programs. These devices and apps may help by providing information and self-monitoring support to survivors in supervised exercise programs, or they may serve as stand-alone intervention strategies for survivors seeking self-directed exercise. Designing such interventions to maximize engagement and effectiveness is a critical research need [47]. All exercise programs for cancer survivors need to be evidence-based and have demonstrated efficacy, effectiveness, and safety, regardless of program type or delivery characteristics.

Medically Based Programs

Cancer rehabilitation can include exercise and conditioning for cancer survivors as well as focused exercises for remediating specific functional problems resulting from cancer or cancer treatment. Cancer rehabilitation is defined as "medical care…delivered by trained rehabilitation professionals who have it within their scope of practice to diagnose and treat patients' physical, psychological and cognitive impairments in an effort to maintain or restore function, reduce symptom burden, maximize independence and improve quality of life." Cancer rehabilitation is ideally integrated into comprehensive cancer care across the care continuum [48]. Cancer- and treatment-related impairments can lead to profound declines in functional health and may increase risk of injury or aggravation of symptoms with independent exercise. Exercise is a foundational component of cancer rehabilitation interventions because of its power to enhance physical, psychological, and social fitness. Downstream, functional fitness underpins successful participation in personal, social, and vocational activities. Medical rehabilitation interventions incorporating exercise have been shown to mitigate many debilitating functional consequences both during and following primary treatment [52].

In clinical practice, cancer survivors present with unique combinations of impairment, compromised functional health, and comorbidities, the combination of which can be resolved into specific components. Rehabilitation interventions are designed to match each survivor's specific functional and life quality needs. Interventions are generally delivered by a multidisciplinary team of rehabilitation professionals and

may include medication, diagnostic and therapeutic procedures, counseling, behavior change, exercise teaching, and physical activity promotion. It is important to recognize that a survivor with no focal impairment or comorbidity may present with profound declines in functional health, such as deconditioning and fatigue, requiring concerted rehabilitation. Medically based rehabilitation programs are thus suited for those survivors with impairments, related functional health declines, or comorbidities [53, 54] that make independent exercise unsafe. As a survivor's health improves and their fitness increases, they may transition to more independent, less supervised settings. In the Rehabilitation and Exercise Oncology model of care (ActivOnco) program, for example, hospital-based physiotherapists identified cancer survivors who needed rehabilitation, and after survivors made gains in functionality and physical performance, they were transitioned to work with exercise specialists in a community-based wellness center, while those without complex comorbidities or limitations were referred directly to community-based programs [55].

One advantage of cancer rehabilitation programs is that when there is a medical indication for treatment, it is often covered by health insurance or health payers. In the USA, cancer rehabilitation is covered as an essential health benefit under the Affordable Care Act, although out-of-pocket cost sharing (i.e., co-pays) and other medical management often apply [56]. However, cancer rehabilitation availability and accessibility may be limited by costs, location, insurance plan, lack of providers with cancer-specific training, and time. Additionally, it is likely not reimbursable for survivors without diagnosable impairments.

Community Programs

Medically-based programs may be limited to people receiving care at major cancer centers. Accessing these programs may be infeasible for many cancer survivors due to impositions including cost, availability of transportation, and time away from work and family. There is increasing availability of programs offered in community settings that can help extend physical activity benefits to these survivors. Community-based programs provide either structured or supervised exercise or training in behavioral skills to increase physical activity. These programs may involve activities done as a group or individual work with an exercise specialist or health educator [57]. Often, these programs are time-limited (e.g., 12-week program), but some programs may have multiple options for participation. There are a growing number of programs specifically targeted to cancer survivors, For example, the YMCA offers the 12-week LIVESTRONG at the YMCA program to cancer survivors. In this program, small groups of cancer survivors attend twice-weekly exercise sessions led and supervised by YMCA trainers [58]. This program has been shown to increase physical activity and improve quality of life and fitness [58]. The program is offered free of charge to survivors. The Livestrong Foundation provides initial start-up money for the program, but the local YMCAs are responsible for ongoing funding. With a growing number of YMCAs offering the LIVESTRONG program

and the vast majority of Americans living in close proximity to YMCA facilities, this program has enormous potential to scale up and meet the needs of many cancer survivors who do not require medically supervised programs. Currently, the program is available in over 800 communities and has served over 70,000 cancer survivors.

Other programs designed for the general population, or for aging individuals, may be appropriate as well and are more prevalent in the community. The National Council on Aging has identified evidence-based exercise programs for older adults that may be offered by senior centers in the community [59]. Community-based programs may be fee-for-service or provided at no cost to the survivor. They are generally not covered by insurance, although some Medicare advantage programs, which offer such programs, reimburse gym memberships.

It is important to develop standards for community programs in order to maximize benefits and minimize risks. Program standards for community settings will help assure that their exercise services are evidence-based and safe for each survivor who may seek them. Connecting survivors with appropriate programs will require highlighting a variety of evidence-based programs on cancer centers' and national nonprofit organizations' websites and publications. A national registry of evidence-based community exercise programs, such as ACSM's Moving Through Cancer initiative [60], can help provide this service for cancer survivors and oncology and survivorship care providers. For many programs, additional research and program evaluation will be needed to bolster program safety and effectiveness, identify which programs are best for different survivors based on their needs and preferences, and test models of program delivery that are efficient, effective, and sustainable.

Home-Based Programs

Home-based exercise programs for cancer survivors can feature a range of guidance and support without the supervision that medically based exercise programs provide. The foundation of home-based exercise programming is providing cancer survivors with information and guidance to help them exercise independently. These services are often provided on a one-time basis (e.g., as patient education information provided by a physician) or as resources that are provided passively, which survivors must take the initiative to access (e.g., information provided on a website). Patients and survivors can receive exercise encouragement and guidance during their healthcare provider visits, but it is unclear whether this alone is sufficient to achieve behavior change in the majority of survivors. In fact, cancer survivors who have reported receiving physical activity advice from healthcare providers in large survey studies demonstrate only modest improvements (4–5%) in likelihood of meeting physical activity guidelines [61, 62]. However, research supports the effectiveness of home-based programs that continue to provide information and active support on an ongoing basis [24, 63–71]. Such programs provide information,

resources, and guidance through print or online materials, particularly tailored materials, telephone coaching, peer support, and devices to support behavior change, such as pedometers, activity trackers, and weights or resistance tubes. Ongoing monitoring of exercise adherence and safety via logs, telephone, or email, coupled with follow-up exercise assessments during clinic appointments, may help increase accountability and motivation among cancer survivors. Recent studies have implemented exercise programs following this model among survivors of breast, colorectal, prostate, lung, head and neck, and pancreatic cancer at various stages of survivorship [72–77].

Are Cancer Survivor-Specific Programs Needed?

One important question is whether it is important to develop lifestyle intervention programs that are specific to cancer survivors or whether survivors should simply use programs available for individuals who have not received cancer diagnosis. Community programs for the general population have been tested for cancer survivors and found to be effective. For example, both Curves and Weight Watchers have shown positive benefits for breast cancer survivors when combined with some cancer-specific content [78, 79]. The answer to the question of whether a cancer-specific program is needed varies from survivor to survivor, depending on the health status, the risk level associated with activity types and modalities, and survivors' preferences and comfort. For example, cancer-specific programs that provide guidance and supervision to minimize risk are favorable for survivors who experience or are at risk for significant treatment side effects including undernutrition, lymphedema, cachexia or sarcopenia, or significant fatigue. Others may warrant high levels of guidance and supervision due to health problems that are exacerbated by prevalent comorbidities. Some survivors, even those with relatively few cancer sequelae, may lack exercise self-efficacy after cancer diagnosis and treatment [80–82]. These individuals may require programs that are tailored to cancer survivors, allowing for survivorship-specific concerns to be addressed while also reinforcing the survivor-specific benefits of increasing physical activity [78].

Within the universe of evidence-based and safe exercise programs for cancer survivors, tailoring program aspects to survivors' preferences may help maximize adherence and benefits. These aspects include the timing of exercise relative to treatment, exercise modality, personnel delivering exercise counseling, level of supervision, independent or group exercise formats, and exercise location [83]. In a systematic review of studies of adult cancer survivors' exercise preferences, Wong and colleagues summarized preferences in 6 key areas: when to start exercise, exercise modality, exercise programming delivery, companion preferences, location, and level of supervision. The modal preferences for each category from the quantitative studies reviewed are summarized in Fig. 18.1 [83]. While a range of exercise modalities and settings have been found to benefit cancer survivors, most studies assessing preferences find that survivors prefer walking for exercise and doing at

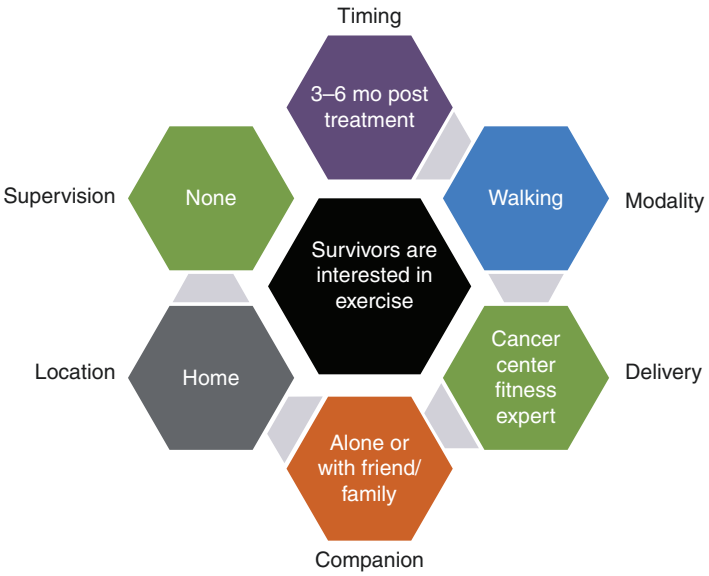

Fig. 18.1 Modal survivor physical activity preferences from a systematic review by Wong and colleagues [83]

home either alone or with a companion, but there is also variability, with some studies indicating preferring gyms, fitness centers, or clinics.

Improve Exercise Screening and Referral Services for Survivors

Clearly "one size does *not* fit all" in identifying the best approach to increase physical activity for a given cancer survivor. Cancer- and treatment-related adverse effects frequently lead to changes in body structure and physiologic dysfunction that may complicate or inhibit recreational activities or even activities of daily living [49–51]. The nature and degree of limitations and impairments are relatively unpredictable if based solely on cancer types and treatments. Personal factors including sociodemographic characteristics and comorbid health conditions may be more predictive of changing functional health status during cancer survivorship than cancer types, stages, or past and planned treatments. These factors need to be integrated into exercise counseling and referrals to exercise programs for cancer survivors [84].

The range of physical and functional limitations among cancer survivors is wide due to interactions between cancer sequelae and personal factors. Some survivors may experience few or no limitations, some experience lingering or late treatment effects such as lymphedema or peripheral neuropathy, and others experience serious

and constant symptoms like cardiomyopathy or severe fatigue. Cancer or its treatment may lead to few ongoing problems for some survivors, but comorbidities such as diabetes, cardiovascular disease, or hypertension may continue to affect physical functioning and quality of life. Obesity is a risk factor for several types of cancer, including endometrial, postmenopausal breast, esophageal, liver, colorectal, kidney, gall bladder, gastric cardia, ovarian, thyroid, and pancreatic cancers, meningioma, and multiple myeloma [85–88]. Therefore, many survivors are overweight or obese prior to diagnosis and remain so after treatment, increasing risk for cardiometabolic disease [89]. Cancer and cancer treatment result in weight gain for some survivors, particularly those entering treatment with normal body mass index. For other survivors, cancer and related treatments result in weight loss, particularly those with advanced disease or experiencing multiple or long-duration therapies.

It is necessary to employ a patient-centered, tailored approach to identify appropriate exercise and rehabilitation support due to the vast differences across the spectrum of exercise services, from independent, home-based exercise to inpatient rehabilitative treatment [90]. Alfano et al. [91] describe approaches to matching impairments with the appropriate levels of supervision and guidance in exercise services. Level I includes survivors who are deconditioned but not experiencing any cancer-specific impairments or complicating comorbidities. Level II includes individuals who have comorbid or other conditions that call for supervised exercise approaches but who lack specific cancer-related impairments. Level III refers to survivors with cancer- or treatment-related impairments but who do not have systemic health concerns that may limit exercise safety, such as cardiomyopathy. And level IV includes survivors with more severe, possibly systemic, symptoms (e.g., persistent severe fatigue or cachexia) or refractory impairments from cancer treatment.

Survivors' goals and preferences are also important in determining appropriate exercise prescriptions or referrals. Based on the guidelines for cancer survivors, it is desirable to encourage survivors to engage in both aerobic and resistance exercise concurrently. However, these are two distinct behaviors, so adopting an exercise program consistent with guidelines is essentially changing multiple lifestyle behaviors, which may be particularly difficult. National survey data indicate that between 24% and 44% of cancer survivors meet aerobic exercise guidelines, whereas 16–31% meet resistance exercise guidelines and only 9–17% meet both guidelines [92]. Establishing the efficacy of multiple behavior change interventions among cancer survivors will require further research [93]. Multiple health behavior change strategies may work for some survivors who are ready and motivated to make lifestyle changes, but others may experience difficulties in developing and sustaining multiple new behaviors simultaneously (particularly considering other survivorship-related behavioral changes that might be needed, such as medication adherence and attending recommended medical appointments).

A systematic review of cancer survivors' preferences for physical activity found that most survivors were interested in being more active, although their preferences were not always aligned with the full complement of exercise in the physical activity guidelines [83]. This review identified 34 studies that assessed survivors' preferences for the type of physical activity, and in 31 of these studies, survivors' preferred

activity modality was walking. Walking may represent a good starting place for a survivor who is just starting an exercise program. Moderate- [94, 95] and even light-intensity [96] aerobic activity is associated with improvements in quality of life, with the addition of strength building exercise potentially coming after the survivor has established an exercise habit. In four of the quantitative studies and two qualitative studies, survivors also expressed a preference for resistance exercise, highlighting the importance of having this option available as well. Behavior change research and theory indicates that incremental behavior changes are more easily achieved than major lifestyle changes. Slow and steady adaptations in behavior can help survivors build self-efficacy, which in turn fosters sustained behavior change [97]. Additionally, intrinsic motivation is a strong predictor of behavioral adherence [98–101], indicating that encouraging a survivor to develop an exercise program around preferred activities is more likely to be successful than imposing a predetermined exercise routine. Creating a patient-centered process for screening and referring survivors to exercise programs necessitates integration of survivors' preferences with information about their impairments, functioning, comorbidities, and access.

Framework for Referral to Appropriate Lifestyle Behavior Services

Cancer survivors have diverse goals and interests, and we need better systems in survivorship care to evaluate and triage survivors to exercise programs that best align with their health conditions, needs, and preferences. In Fig. 18.2, we propose a framework for referring cancer survivors to appropriate services based on physical condition, preferences, and goals. Recent guidelines for the general population have taken into account the possibility that recommending physician clearance before exercise for all individuals, or a supervised structured program, may pose a barrier to starting an exercise program, which could potentially result in more harm than benefit [102]. Given that most survivors indicate they prefer to exercise on their own [83], the focus of this framework is to identify the "least restrictive alternative" for a given survivor's referral to exercise services in terms of levels of required medical screening and supervision. With this in mind, it is important to establish that the framework does not aim to recommend against more intensive or supervised services for a given survivor; instead, we aim to establish safe and feasible "starting places" for specified levels of exercise intervention. For example, many survivors can benefit from decreasing sedentary behavior by introducing short bouts of light- and moderate-intensity lifestyle activity throughout their days, and this behavior change can safely take place without medical screening or supervision. On the other hand, a survivor with significant adverse effects from treatment, cancer-related symptoms, or significantly compromised functional health should consult physicians before engaging in moderate to vigorous aerobic activity or resistance training. For survivors without the presence of any of these and with well-managed

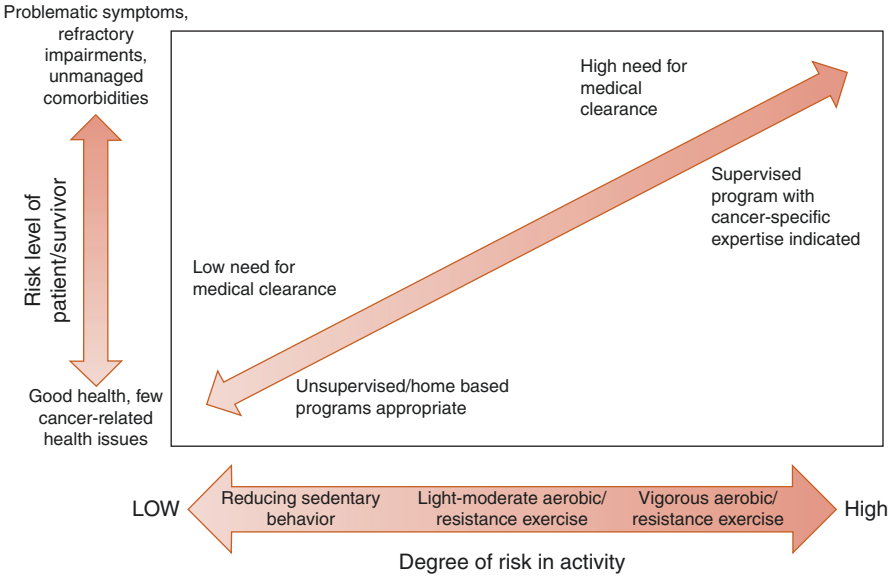

Fig. 18.2 Patient-centered, tailored framework for identifying appropriate physical activity/exercise programming for cancer survivors. The framework takes into account both survivor health condition (risk level) and goals and preferences. Programming types identified represent a reasonably safe starting place for survivors, although it may be possible that more intensive services could be beneficial for the survivor

comorbidities (e.g., well-controlled hypertension), it is generally safe and effective to participate in self-directed moderate-intensity aerobic exercise at home, in neighborhood environments, or in a community facility or program. Survivors with unmanaged comorbidities, or those who plan to engage in higher-intensity exercise that entails more risk, should undergo more intensive medical screening. Higher-risk physical activity for these survivors should be supervised and guided by medical or exercise professionals initially.

Individuals other than physicians and nurses may be enlisted in the assessment and referral of cancer survivors to exercise programs. Patient navigators, health educators, and community health workers, for example, may be effective in motivating cancer survivors to engage in home-based physical activity or access exercise services. Stout and colleagues describe a clinical pathway to expedite screening and referral to rehabilitation services early in the cancer continuum, helping prevent disability and loss of function during cancer treatment. In their model, a patient navigator with experience in rehabilitation follows patients for the duration of their cancer care, assessing changes in physical functioning and triaging survivors to receive general exercise encouragement and advice, referrals to community-based programs, or referrals to skilled rehabilitation interventions [103]. With the complexity of cancer care, there is a rising need for nonclinical personnel to have defined roles that involve facilitating access to and providing exercise services.

Implementation of screening strategies using this framework can help connect survivors with services tailored to their goals and personal needs to increase physical activity without introducing additional barriers (e.g., needing to attend specific programs at designated times and places) that might deter or limit participation.

Expand Dissemination and Implementation Research to Test Service Delivery Models for Evidence-Based Exercise Interventions

Dissemination and implementation (D&I) research is a critical need to assure that the results of physical activity research among cancer survivors are translated into programs that are available to all survivors who need to access them. Dalzell and colleagues recently described a large study involving implementation of the Rehabilitation and Exercise Oncology model care (ActivOnco) with the goal of providing appropriate exercise prescription to cancer survivors with varying degrees of performance status and various cancer diagnoses and stages. The model demonstrated broad reach (1635 patients with 13 different cancer diagnoses) and success in providing education regarding physical activity guidelines, functional assessments, and referrals to wellness center services, home-based exercise programs, and skilled rehabilitation services. However, lack of funding and physical and human resources posed barriers to the implementation [55]. According to a recent portfolio review of the National Cancer Institute grants on lifestyle interventions in cancer survivors, there is a great need for additional D&I research in the area of exercise and cancer survivorship [104]. Models of effective screening for and referral to physical activity programs are needed for survivorship care, and effective and dispersible program models need to be refined and tested in other settings and survivorship groups. Efficacy studies involving physical activity and cancer survivorship to date have focused on internal validity, with little attention on how programs might be implemented in real-world settings.

Frameworks such as reach, efficacy/effectiveness, adoption, implementation, and maintenance (RE-AIM), provide useful tools for studying the population impact of various implementation models [105]. Pullen and colleagues utilized the RE-AIM framework to examine the potential for Project MOVE, which aims to increase physical activity among breast cancer survivors, to translate from research to community practice [106]. The authors identified individual tailoring of physical activity programming to survivors' needs and preferences and allowing for gradual transitions to exercising independently as important components for successful community implementation [106]. Eakin and colleagues are also employing RE-AIM to evaluate broad dissemination of a telephone counseling-based exercise intervention among 900 Australian cancer survivors [107]. These researchers have leveraged relationships with important community-facing partner organizations

focused on cancer control in order to maximize reach and improve the feasibility of widespread implementation [107].

Beidas et al. examined the potential for the Physical Activity and Lymphedema (PAL) strength training trial for breast cancer survivors to translate to an outpatient rehabilitation setting for sustained delivery [56]. The safety and effectiveness of the original PAL intervention were maintained, helping to inform larger-scale dissemination of strength training interventions for breast cancer survivors [56]. Challenges in the Strength After Breast Cancer implementation trial included the new group format of intervention delivery for providers, distance to intervention sites for participants, and costs of delivery for both providers and participants. Cost of strategies to increase uptake of exercise among survivors is frequently an important consideration for program dissemination and implementation. Mewes and colleagues (2017) modeled the cost-effectiveness of implementation strategies to increase physical activity uptake among cancer survivors [108]. Six of these strategies were directed at healthcare providers: developing and implementing reminder systems, identifying local opinion leaders, holding continuing education meetings, conducting educational outreach visits, performing audits and providing feedback, creating printed educational materials, and performing a combination of strategies. Two strategies were directed specifically at patients: offering a motivational program and providing financial incentives. Mewes and colleagues found that all strategies except for providing patients with financial incentives were cost-effective in the model, with utilization of provider reminder systems, engaging local opinion leaders, and implementing a patient motivational program showing the highest benefits [108].

Pinto, Stein, and Dunsiger tested a community-based implementation model of an evidence-based program to assist breast cancer survivors in increasing physical activity [63]. In this study, 18 breast cancer survivors from the ACS's Reach to Recovery program acted as "peer volunteers" and received training to deliver a 12-week telephone-based physical activity promotion program to 76 breast cancer survivors. Peer mentors were effective in increasing participants' physical activity relative to other breast cancer survivors in a contact control condition [109]. This community-based intervention, utilizing peer volunteers, provides an important example of scaling up an intervention beyond its original research setting and increasing its reach through collaboration with a well-established community-based organization.

Efforts to evaluate physical activity interventions for cancer survivors outside of research settings have begun, with D&I researchers leading the way [56, 69]. However, additional systematic efforts are needed to achieve widespread dissemination of active lifestyle to promote recovery of physical functioning and quality of life in cancer survivorship. Figure 18.3 summarizes components needed to advance implementation of exercise programming in cancer care. D&I researchers and partners from community and clinic settings who are interested in this field can find evidence-based interventions and guidance for implementation on national websites (e.g., Cancer Control P.L.A.N.E.T and the Research-tested Intervention Programs). As such, all researchers developing and evaluating exercise interventions for cancer survivors should be encouraged to post their interventions and contribute to this resource. In addition to studying the dissemination and implementation of existing

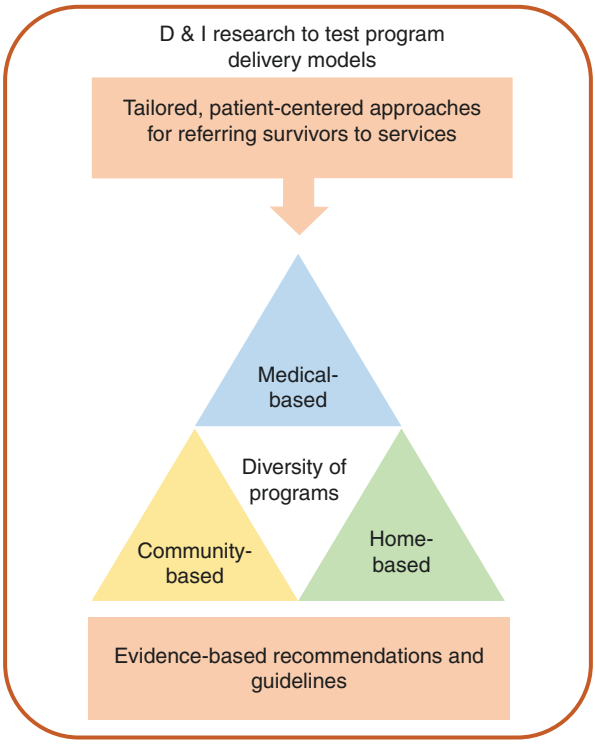

Fig. 18.3 Summary of components needed to advance implementation of exercise programming in cancer care

interventions, we recommend that researchers planning new studies on physical activity among cancer survivors consider external validity, dissemination, and the potential for sustainability. In doing so, researchers will be developing programs and collecting data that can be more appropriately generalized to the broad population of cancer survivors. There is also value to exploring the contexts of community oncology clinics and primary care settings for programming in physical activity and cancer survivorship. These practices may provide valuable settings for implementing and sustaining physical activity programs for cancer survivors, but little is known about their potential to do so.

Conclusion

Many factors and components must be addressed to ensure that cancer survivors' needs for exercise services and support are met. Research gaps must be addressed with added D&I research with the goal of optimizing care and health outcomes for the broad and diverse population of cancer survivors. Critical components of

assuring access to quality exercise programming and support also include the need to expand the availability of diverse, evidence-based exercise programs for cancer survivors with various needs and preferences and to improve patient-centered screening and referral to physical activity services. Addressing each cancer survivor's needs for living physically active lifestyles will help ensure that cancer survivorship is long and marked by optimal health.

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Chapter 19
Viewing Exercise Oncology Through the Lens of Multidisciplinarity

Martijn M. Stuiver

Introduction

From the previous chapters, it has become evident that physical activity, and exercise in particular, is important throughout the cancer care continuum; exercise may help patients prepare for treatment [1–3], and exercise can help reduce treatment-related side effects during and after treatment [4, 5], maintain or regain an acceptable level of functioning and quality of life [6], and reduce the health risks related to late effects [7]. Thus, all individuals with cancer should be encouraged to be physically active, and to start or continue exercising [8, 9].

One might argue that exercising, like healthy eating, is a lifestyle choice, instead of a responsibility of the health-care system. However, from the previous chapters, it has also become clear that exercising for individuals with cancer is often easier said than done. Even for people without cancer, there can be many barriers to exercising, in many dimensions. Barriers can be practical, social, psychological, behavioral, or physical or a combination of those [10, 11]. Being diagnosed with and treated for cancer is not going to diminish any of those barriers and is likely to add a few. Therefore, to become or stay physically active, including starting or continuing structured exercise, many individuals with cancer will at some point need the support from health-care professionals (HCPs).

Exercise support can take many forms, ranging from providing print materials with information on the benefits of physical activity or on how to perform exercises, all the way up to supervised exercise as part of full multidisciplinary cancer

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rehabilitation. Exercise support can also be delivered by a wide range of professionals. Within the context of medical care, physical therapists, occupational therapists, clinical exercise physiologists, physiatrists, sports physicians, behavioral psychologists, and nurses or nurse practitioners all can be involved to support exercise in one way or another. While there are good reasons to involve health-care professionals to support exercise and physical activity behavior of patients with cancer, at the same time, care must be taken to avoid over-medicalization of exercise. Patients and survivors who are able to exercise without supervision or other interference of health-care professionals should be empowered to do so. In the community, exercise physiologists and fitness professionals can support patients to increase or maintain their physical activity level and physical fitness, provided that they are sufficiently knowledgeable about the consequences of cancer and cancer treatment. To support exercise in such a way that it aligns with patients' clinical state, circumstances, preferences, values, and beliefs, there is no one-size-fits-all solution. Also, there is considerable overlap in the domains of various health professions, which means that there is no general rule to determine who should do what when it comes to delivering exercise support – unless, of course, specific skills or knowledge are required that are unique to a profession. Thus, to determine the best way to support individual patients in their endeavor to start or continue exercising during or after cancer treatment, exercise should be viewed through a lens of multidisciplinarity.

A second reason to view exercise through this lens of multidisciplinarity is the multidimensional nature of the barriers for physical activity and exercise that individuals with cancer can experience. Barriers are also not static; they will arise, evolve, and maybe even disappear again, throughout cancer treatment and survivorship. Professionals, be they health-care providers or exercise professionals in the community, need to be able to recognize these barriers and act on them timely and effectively. The same is true for recognizing and utilizing potential facilitators. Health-care providers are well trained to do so, within the context of their own profession. However, they should also have a grasp of how certain barriers might be successfully addressed by involving or referring to other professionals. Most of all, they should be able to discuss the available options of exercise and physical activity support with patients, and provide advice, while recognizing and respecting the preferences and values, as well as the clinical and practical context, of each individual patient.

The objective of this chapter is to discuss how a multidisciplinary perspective on exercise for health is useful to successfully support physical activity or exercise for individuals with cancer, in different phases of cancer treatment and survivorship.

Contextualizing Exercise

The Ability to Adapt

Obviously, the objective of health care is to improve health. Health has traditionally been defined as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." More recently, Huber et al. stated that in

the current era, in which many people live with chronic conditions, such a state is likely unattainable for many. Instead, they proposed to consider health as "the ability to adapt and self manage in the face of physical, psychological, and social challenges" [12].

Adaptation is a familiar concept in exercise physiology. Muscles and bones grow stronger, and maximal oxygen uptake increases, as a result of adaptation to adequate exercise stimuli. Individuals can also learn to cope with maladaptive or dysfunctional organ systems related to physical activity, by learning alternative ways to move or by increasing the capacity of one system to compensate for the failure of another. For example, if exercise capacity is decreased because lung volume and compliance are irreversibly impaired due to surgery and radiotherapy for lung cancer, there is no room for local adaptation (as the damaged lung tissue cannot be trained back to health). However, muscle strength of the breathing muscles can still be optimized to improve respiration efficiency, and peripheral muscle strength, efficiency, and local endurance of other skeletal muscles can be optimized, for example, to improve walking ability. In this case, increasing the capacity of the musculoskeletal system can compensate, at least in part, the structural damage of the lung tissue and function.

Adaptation, or maladaptation, can also occur on a psychological or behavioral level. After a cancer diagnosis, people have to psychologically adapt to the distress caused by the diagnosis. In relation to exercise, psychological maladaptation can occur in the form of fear to physically exert oneself, because signs of exertion such as increased breathing frequency or post-exercise muscle aches are perceived as threatening. This can then be a barrier to physical activity [13]. People who experience steep declines in physical fitness, due to the disease or its treatment, need to adapt to this new reality by altering their behavior; that is, they need to adapt their pattern of spending the available energy in such a way that they can make it through the day. Maladaptation in the form of inadequate activity regulation can be a driver for chronic fatigue [14, 15] and eventually lead to physical inactivity when people stop trying. Sometimes, adaptations with regard to societal roles (i.e., work) or the physical environment are needed in order to enable acceptable functioning. All this illustrates that the concept of "the ability to adapt" is particularly suited to the context of cancer rehabilitation.

ICF

Another useful concept to contextualize exercise in cancer care is the International Classification of Functioning, Disability and Health (ICF). ICF adds to the International Classification of Disease (ICD) by regarding a health problem from the perspective of the impact of a disease or health condition on human functioning. It does so by describing human functioning in domains of anatomical structure and functions, activities and participation, and personal and environmental characteristics. The ICF distinguishes capacity (reflecting what an individual can do in a standardized environment, e.g., walking ability as evaluated with a 6-minute walking

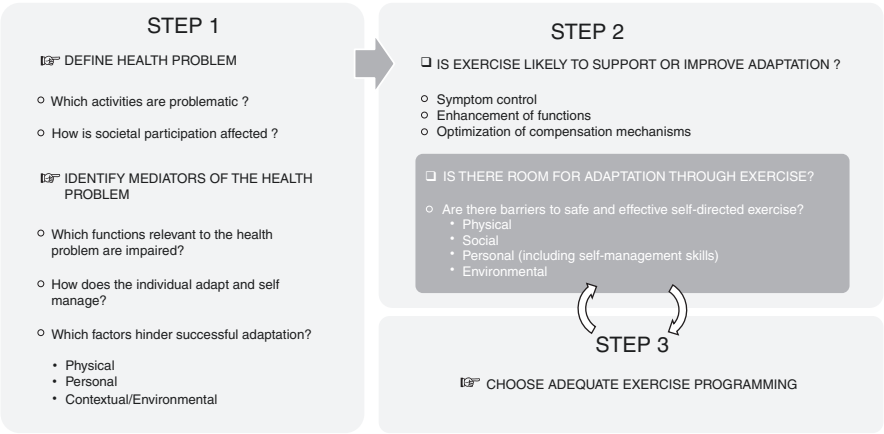

Fig. 19.1 The three-step approach to choosing appropriate exercise programming

test) from performance (reflecting what an individual actually does in his or her usual environment, e.g., the ability to walk from home to the nearest metro station). Discrepancies can exist between capacity and performance. By recognizing the nonlinear interplay and interactions within and between the different ICF domains, one can understand a health problem from a biopsychosocial perspective and decide on health-care interventions accordingly [16].

The ICF and the concept of the ability to adapt complement each other strongly. To understand a health problem, and to help deciding on interventions, a three-step process can be followed (Fig. 19.1). Step #1 involves recognizing the overall health problem and identifying the factors that are related to that health problem ("mediators") in each domain of ICF. If there is maladaptation to these problems, in step #2, the "room for adaptation" is evaluated. This involves assessing the current capacity and performance of the individual and evaluating his or her possibilities to improve or maintain his or her capacity or performance, which includes the identification of barriers and potential facilitators for successful adaptation. In step #3, interventions are chosen. These interventions are aimed at improving the individuals' adaptation by increasing or maintaining his or her capacity, optimizing his or her performance, diminishing (biological, psychosocial, or environmental) barriers, and/or creating or capitalizing on existing facilitators.

Following this process, exercise could be considered as an *intervention*, when step #1 reveals symptoms or impairments that might be alleviated through exercise. If, in step#2, we decide that exercise is indeed a suitable intervention, an evaluation should be made to decide whether or not the patient is able to exercise safely and/or effectively on his or her own. This includes not only an evaluation of the prerequisites for successful physical adaptation to the exercise stimulus, such as anatomical

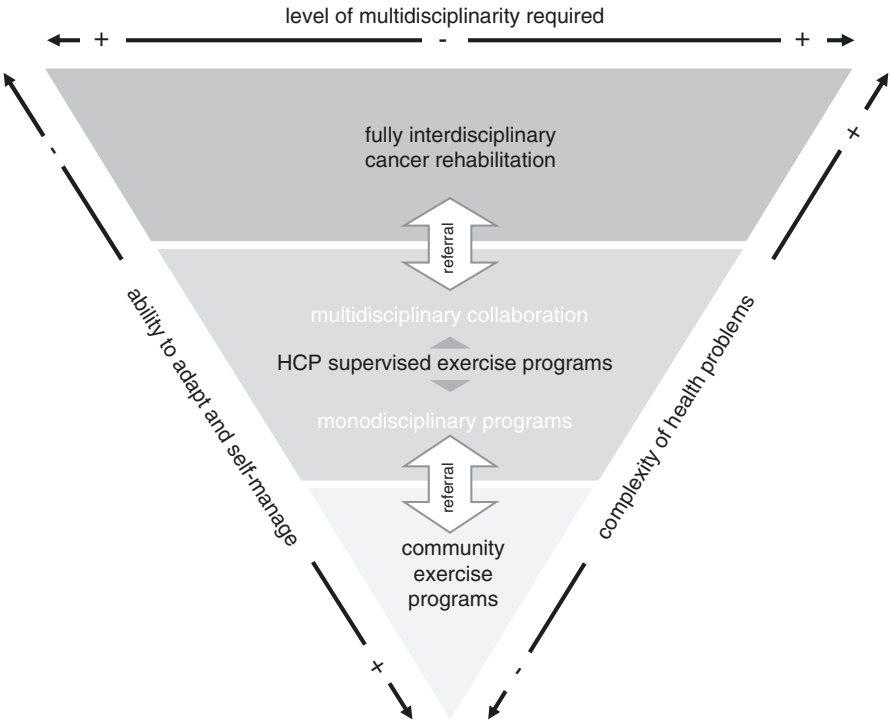

Fig. 19.2 The level of health-care professional (HCP) involvement, and multidisciplinarity required, is dependent on the presence and complexity of health issues and on the individual's ability to adapt to and self-manage. Referrals up and down the chain of exercise programming can be made accordingly

integrity, or nutritional status, but also an evaluation of self-management skills (Fig. 19.1). Finally, in step #3, these considerations are synthesized, leading to referral to appropriate exercise programming (Fig. 19.2). The choice for the appropriate type of exercise program (i.e., the level of health-care involvement) should be periodically reevaluated, and referrals up and down the chain should be made if necessary.

If physical activity is not the *intervention*, but the intended *outcome* – i.e., when not being able to be physically active on the desired level is the health problem addressed or when activity promotion is part of a secondary prevention approach – the same three-step process can be followed. In this situation, mediators identified in step #1 would in fact then be the factors that restrict the ability to be physically active (dark gray box in Fig. 19.1).

Multidisciplinarity

The level of multidisciplinary involvement required can be seen as a function of the level of complexity of health problems on the one hand and the ability to adapt and self-manage on the other (Fig. 19.2).

For example, if, shortly after cancer treatment, a patient is found to be malnourished as well as deconditioned, a dietitian would need to be involved to treat the malnourishment, in order to enable successful physical adaptation to the training stimulus applied to improve exercise capacity. In that case, the dietitian and the physical therapist or clinical exercise physiologist need to coordinate their interventions for optimal effect. Once the nutritional status is stabilized and the individual is capable of maintaining his or her own exercise behavior, referral to community exercise programming (or self-directed exercise) would be warranted. One could also imagine a patient whose health problem is an inability to be physically active on any level because of chronic severe fatigue. Let's assume that the most important mediators for this chronic fatigue are anxiety disorder and depression, in combination with kinesiophobia. It is likely that this individual is physically deconditioned and that exercise will improve the fatigue. However, there is also room and need for adaptation in other areas: the depression should be treated, and the patient should learn to effectively cope with feelings of anxiety. Hence, referral to a health psychologist for counseling or cognitive behavioral therapy might be considered for this individual, in addition to a graded physical activity program. In the community setting, a breast cancer survivor exercising in a local gym may at some point in time develop lymphedema. This condition should be managed by a specialized physical therapist. The sports instructor should therefore recognize the need for referral as soon as this individual complains about feelings of swelling and heaviness. The physical therapist, in addition to starting lymphedema treatment as needed, needs to brief the sports instructor with regard to if and how the exercise program should be adapted for this individual, in the presence of lymphedema. If a health problem is very complex, and several interrelated physical, psychosocial/behavioral, and environmental issues need to be addressed simultaneously and coherently, interdisciplinary rehabilitation by a dedicated oncology rehabilitation team is recommended. Figure 19.3 provides some exemplary clinical vignettes to illustrate the type of cases that would match the various levels of multidisciplinarity.

In the remaining part of this chapter, the multidisciplinary approach to exercise oncology and cancer rehabilitation will be illustrated in more detail. A number of cases will be discussed, looking at exercise through the lens of multidisciplinarity and applying the process described above.

Case 1

C., a senior financial consultant employed by a large firm, was 43 when she was diagnosed with stage II breast cancer. The tumor was HER2 negative and ER positive. When she got her diagnosis, C. was shocked. It struck her as unfair that she should have cancer; she had always been minding her health. She used to exercise regularly; two times per week she made a 45-minute run through the park, and she took spinning classes once a week at the gym. She adhered to a healthy diet, had never smoked, and was not a heavy drinker. Being very successful in a competitive field of work, she had come to believe that through hard work and dedication, one can achieve anything. She had always made her own choices in life, deliberately and with confidence, and she was not one to crumble under pressure. But this diagnosis completely swept her off her feet. Looking back, she explains that she saw no other option but to "surrender her body to the doctors and just wait for it to be over."

She went through neoadjuvant chemotherapy treatment with Adriamycin®, cyclophosphamide, and Taxotere® (AC-T) and underwent breast-conserving surgery with a sentinel lymph node biopsy procedure, which was negative. Post-surgery, she received radiotherapy to the chest wall and anti-hormonal treatment with tamoxifen. Her treatment had been successful, the doctor had said, and her chance of survival is high. Relieved, she returned to work as soon as she could, with a desire to put this episode behind her. Soon, she found that she was not able to concentrate very well. Also, she was tired all the time, and sometimes it felt as if, without warning, all her energy would drain from her body. She did not sleep very well and she increasingly had trouble getting up in the morning. At times, she would wake up in the middle of the night, with a rushing pulse, feeling anxious, but not quite able to discern why. Four months after returning to work, she had to call in sick. She has not resumed working ever since. Her fatigue and sleeping problems have not improved since; she regularly needs to take a nap during the day but at the same time has trouble sleeping at night. When she lies awake, she finds herself worrying about the future, in particular with regard to her work ability. Her fatigue also restricts her in her social activities; she simply does not have the energy left to go out with friends in the evening.

She recognizes that the treatment has taken its toll on her body and that this is part of the problem. At times, she tells herself she should start exercising again, but she can't get herself to do it. Actually, she is not even sure that it would be a good idea, considering how tired she already feels after completing her daily chores, while she is not even working, and considering the pain she feels in her joints at times. On the other hand, she has also noticed that she is starting to put on weight, which she believes is probably due to her diminished physical activity.

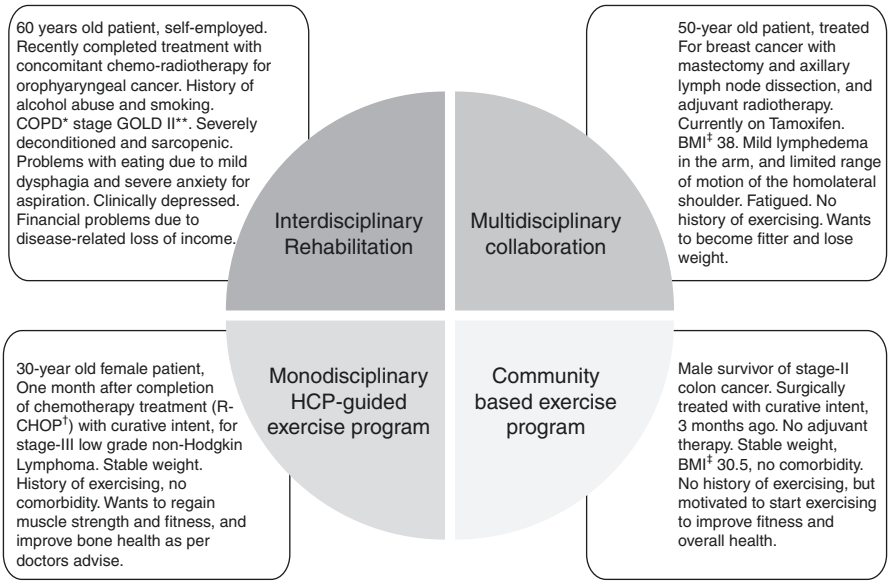

Fig. 19.3 Levels of multidisciplinarity with corresponding exemplary patient vignettes: ∗Chronic obstructive pulmonary disease; ∗∗Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II reflects moderate airflow limitations, 50% ≤FEV1 <80% predicted; †R-CHOP, combination therapy of doxorubicin, cyclophosphamide, vincristine, and rituximab; ‡ BMI, body mass index (kg/m^2)

Looking at C.'s case, it is clear that she has not adapted very well in many domains of ICF: on the level of physical functions, she is deconditioned, fatigued, and putting on weight and has sleeping problems. On the level of activities and social participation, she has had problems with activity regulation and has now become largely inactive. Her role functioning (work) is severely restricted. Also, it seems as though there are several personal factors that hinder successful adaptation, which include not knowing what is the right course of action or even fear of making matters worse. An environmental factor at play is her highly demanding work setting, which requires her to be focused and fully dedicated.

Exercise Support During Treatment

In hindsight, could more attention to supporting C.'s self-management at the time of diagnosis and during treatment have made a difference? Would participation in an exercise program at that time have been useful to improve her ability to adapt and support her health? Looking at the evidence about exercise during breast cancer treatment, it seems that this could indeed have been the case. Taking part in an exercise intervention during chemotherapy would likely have prevented her physical deconditioning and would have attenuated fatigue [17].

Clearly, at the time of diagnosis and treatment, there were some barriers to exercising that would have needed to be addressed. First of all, C. did not adapt very well to the emotional distress the diagnosis caused her and lost her sense of self-efficacy. At this stage, aside from providing psychological support to cope with the emotional distress of the diagnosis, C.'s self-efficacy could have been strengthened by empowering her to stay physically active, instead of "surrendering her body to the doctors and waiting for it to be over." At diagnosis and throughout cancer treatment, the role of the primary health-care providers, the doctor in particular, is of pivotal importance in exercise promotion [18]. C's oncologist could have asked her about her current physical activity, and have encouraged her to stay physically active, explaining that this was something she could do to herself to improve her treatment outcome and manage the symptoms that she was going to experience [19].

The same applies to the nurses and nurse practitioners that C. encountered during her neoadjuvant treatment. Even better, the oncologist could have actively referred her to a supervised exercise program, as the outcome of supervise exercise tends to be better compared to unsupervised exercise [20]. Still, considering her history of exercising, and her low-risk profile at diagnosis, this might initially have been a community program. On the one hand, C. merely needed to be informed of the value and possibilities of exercise and to be reassured that it was safe to continue her regular exercise for now. On the other hand, her treatment with chemotherapy and the subsequent surgery would put her at risk for upcoming physical problems that might impede successful exercise and for developing symptoms that would require adjustments to the exercise program. Managing these issues would require the competencies of a health-care professional, such as a physical therapist, with sufficient oncological knowledge. So, referral to a clinical exercise program might also have been considered. Alternatively, a *combination* of community-based exercise with low-frequent support and advice from a physical therapist with oncological knowledge might have been enough to keep C. largely self-managing her exercise program. Additionally, such prospective surveillance by the physical therapist would have ensured timely health-care interventions to help manage new physical problems, should these have arisen [21]. Throughout treatment, regular inquiries about C.'s physical activity level by the doctors, nurse practitioners, and nurses would have affirmed her belief of the importance of exercising, which would have helped her to adhere to the exercise program [18].

So, viewing through the lens of multidisciplinarity, exercise support for C.in this stage of cancer treatment would have required the involvement of physicians, nurses, and nurse practitioners, to increase awareness and express support, and from a physical therapist working together with a community exercise professional, referring back and forth as needed, to optimize the exercise program.

Exercise in the Context of Rehabilitation

As described in parts II and III of this book, in the early stages of the cancer care continuum – that is, at diagnosis as well as during and shortly after medical treatment – exercise-based rehabilitation is often impairment driven [22]. During

treatment, a major focus of exercise is on maintaining physical function, improving treatment tolerance, and controlling symptoms. Shortly after treatment, rehabilitation is aimed at regaining and/or improving physical functions to at least the level where survivors can engage in their regular activities of daily living. Exercise interventions in these phases may be generic (i.e., aimed at exercise tolerance in general), therapeutic (i.e., aimed at restoring shoulder function), or both. Exercise prescription factors (e.g., frequency, intensity, time, and type) and temporization are chosen to optimize the physiological stimulus, taking into account the influence of cancer treatment where appropriate. Success might be declared when symptom management is adequate and physical capacity and performance are maintained or improved. However, when a health problem provoked by the cancer treatment manifests itself not only on the level of functions but also on the level of activities and/or societal participation, additional considerations need to be made.

For an exercise program to improve a specific activity of daily life, it is not sufficient to simply improve exercise capacity in general. Just like a sports-specific exercise prescription is needed to improve jumping for a basketball player or pitching for a baseball player, a functional approach to exercise prescription is needed to improve regular activities of daily life [23].

Case #2

Mrs. R. is an older female patient who has been hospitalized for several weeks after treatment with lower abdominal surgery for ovarian cancer. This was followed by adjuvant chemotherapy. Mrs. R. lives on her own in her home and never had to rely on help from anyone. She regards her independence as a very important value in life. Now, she feels insecure when moving about, and she is quickly fatigued. This means she cannot undertake the physical activities that she used to do – in particular, working in her garden. Working in her garden involves, among other movements, being able to kneel and get up again and working with her arms overhead – body movements from which she now experiences physical limitations. Due to the treatment and her general inactivity during treatment, she is deconditioned. In addition, she now suffers from a limited range of motion of the shoulders; lack of strength in the arms, shoulders, and lower extremities; and lack of balance. This is making her insecure, and she is afraid to use a ladder to reach the higher branches of the trees she needs to prune. She has tried several times to do some gardening work, but she was exhausted afterward and dissatisfied with what she had been able to achieve, as she also has other daily chores to do, such as tidying the house. She currently no longer takes care of the garden herself, instead relies on the help of a professional gardener. Consequently, she is less physically active. Also, the need to hire a gardener is bothering her, as she loved to be busy outside and because she does not want to have to rely on others. Her rehabilitation goal is therefore to take care of her garden by herself once again.

Multidisciplinary Collaboration

In the example of Mrs. R., a high-intensity interval training program on a stationary bike and a circuit of six strength exercises for all large muscle groups are probably not going to help her achieve her goal – even though it will likely result in improved overall physical fitness. Rather, it would be useful to first observe *how* exactly Mrs. R. is normally doing her gardening work and what she needs to be able to conduct this again in a satisfactory manner. On the level of *capacity*, there may be room for adaptation in terms of improving physiological functions. Exercises to improve muscle strength of the trunk and lower and upper extremities, and therapeutic exercises to increase the mobility of her shoulders, could be the starting point of an exercise program, as offered by a physical therapist. The type of strength training should of course be aligned with the rehabilitation goal. For example, for the shoulder muscles, increasing muscle endurance is much more relevant to the rehabilitation goal than increasing maximum strength. Increasing maximum grip strength may be useful, however. But the rehabilitation plan does not end with improving the basic physical functions. As functions improve, exercises should be added that mimic the actions Mrs. R. needs to perform when working in her garden. Such functional exercises are intended to improve *performance* in addition to capacity. These exercises should also be gradually increased in intensity and complexity to maintain the progressive overload needed to trigger adaptation. Such an approach will ensure sufficient specificity of the exercises and, additionally, help build Mrs. R.'s self-confidence in performing her gardening activities. On the level of performance, there may also be room for adaptation in other areas that do not even require improvement of exercise capacity. For example, Mrs. R. could maybe change her (movement) strategies to improve the ergonomics or safety of certain actions. Maybe she could partition and alternate the gardening activities in such a way that they would require less energy. Also, there may be possibilities to improve performance of her gardening activities by changing environmental factors, such as equipment used. An occupational therapist may therefore offer valuable insights, both to the patient and to the physical therapist [24]. The occupational therapist should make sure that the physical therapist is informed about the advice provided. In this way, the physical therapist can shape the functional exercises in such a way that they align with the instructions of the occupational therapist regarding how Mrs. R. can perform her gardening activities most safely or economically. As soon as her capacity and performance (in terms of functions and skills) start to improve in the rehabilitation environment, Mrs. R. needs to practice her activities in real life too, gradually taking up her gardening again. If needed, the occupational therapist may also play a role in this phase by helping Mrs. R. to plan her gardening activities carefully, in such a way that she has sufficient energy left to engage in other activities of her daily life and sufficient time to rest and recover. To do this effectively, the occupational therapist needs to be informed by the physical therapist about the current capacity of Mrs. R.

In this example, *multidisciplinarity* translates into two health-care professionals, a physical therapist and an occupational therapist, who collaborate to benefit from each other's expertise while they both contribute to help a patient achieve a single, relatively low-complex rehabilitation goal.

Interdisciplinary Rehabilitation

A limited number of patients may develop more complex, interrelated problems in several domains of functioning (physical, psychological, social), to such a degree that these issues need to be addressed simultaneously and coherently. Usually, this requires a much more intensive collaboration of several health-care professionals in an interdisciplinary oncology rehabilitation team [25]. Like rehabilitation for other chronic health conditions, such cancer rehabilitation often uses a goal-directed approach. That is, in a process of shared decision-making, patients first prioritize the problems that they experience and want to improve through rehabilitation. Next, they set a number of specific goals they want to achieve, which are formulated and operationalized at the level of activities and societal participation. Finally, a treatment plan is developed to achieve those goals, for example, using the three-step approach described earlier to identify and address the key factors to successful adaptation. The treatment plan involves actions from several health-care professionals, which need to be closely aligned. As a result, it may happen that, instead of being designed to achieve optimal physiological capacity and specific functional performance, the exercise prescription needs to be adapted to accommodate the overall team strategy. For example, the team may decide on a general treatment strategy of diminishing anxiety, increasing self-efficacy and behavioral control, and improving self-management through graded exposure to activities of daily living. This then implies that the exercise program that is part of the multidisciplinary intervention is progressed much more slowly than would be desirable from an exercise physiology point of view.

C.'s case is a good example of a health situation in which the level complexity and interrelatedness of the problems may initially require such a comprehensive approach to rehabilitation. C. has problems in several areas of functioning: she has physical limitations (deconditioning, weight changes, joint pain), psychological issues (anxiety, low self-efficacy, and problem-solving ability with regard to her activity levels), cognitive problems, and role-functioning problems with regard to work and social interactions.

All of these problems are connected in several ways: her anxiety, her worries about her work ability, her dysregulated sleeping pattern, and her low physical activity level all maintain her sleeping problems. Her deconditioned state, physical inactivity, sleeping problems, and anxiety are drivers for her fatigue. Fatigue, anxiety, and cognitive problems (concentration) may also very well be interconnected. Finally, her low self-efficacy, fatigue, and joint complaints are important barriers to exercising.

So, C. is enrolled in a cancer rehabilitation program. Because some of the physical problems she is experiencing may be related to treatment side effects, she is medically screened by a physiatrist and an oncologist. She gets a cardiopulmonary exercise test with ECG and breath-by-breath gas exchange to rule out cancer treatment-induced cardiac problems that may underlie her fatigue and exercise intolerance and to obtain a good starting point for prescribing aerobic exercise. The joint problems are recognized as related to the anti-hormonal treatment, and inflammatory joint problems are ruled out. The physiatrist explains that exercise is likely to improve these complaints and will not increase them [26]. Through shared decision-making, C. and the rehabilitation team set several goals for the rehabilitation. The most important goals are (1) to take up self-directed exercise again, (2) to self-manage daily chores and activities while maintaining sufficient energy for social activities in the evening, and (3) to make a start with return to work. Several disciplines will be involved: The psychologist will be treating the anxiety disorder and help C. with getting a grip on her thoughts and worries. The occupational therapist will first address sleeping behavior and teach relaxation exercises. The occupational therapist will also work with C. to help her regulate her activities (including those activities related to the rehabilitation program) adequately. In the next step, the occupational therapist will support C. to take control in developing a work reintegration plan together with the occupational physician at her workplace. The physical therapist will start with an exercise program, which will have two major goals. The first goal is to improve exercise tolerance and physical functions such as increasing aerobic fitness and muscle strength. To achieve this, in the first weeks, C. will be coached to increase her physical activity level using home-based walking and moderate-intensity strength exercises, as well as twice-weekly moderate-intensity exercise at the rehabilitation facility. Next, a nonlinear exercise prescription for aerobic training, incorporating high-intensity interval training [27, 28], will be employed, in addition to progressive strength training based on repeated one repetition maximum tests. The second goal of physical therapy is to improve exercise self-efficacy and self-management. To achieve this goal, C. will be educated on general principles such as overload vs rest, and temporization, and learn to recognize signals of overexertion (topics that are also addressed during the occupational therapy sessions in the broader context of daily functioning). Also, weekly exercise goals are set and documented in an exercise log, so C. can track her improvement. The exercise program will start generic and will be made more specific to C.'s own preferences with regard to self-directed exercise, i.e., running. Because regular strength exercises are recommended for breast cancer survivors [29], C. will also be taught strength exercises using body weight, which she can implement in her own training schedule. Participation in a group-based sports/game module, led by a dedicated sports instructor, will also be part of the rehabilitation program. The main goal of this module is to have C. exercise in a way that is fun and challenging, while the games used are also designed to help participants improve their self-management and self-efficacy. Finally, a dietitian will be consulted to evaluate whether adjustments are needed to C.'s diet, in addition to her exercise program, to manage her weight [30]. The rehabilitation team expects that goal attainment will be achieved within 15 weeks.

This is just one example of the interdisciplinary approach to cancer rehabilitation. Other types of interventions, including different exercise prescriptions, and other combinations of disciplines involved may be applicable for different individuals. For some types of cancer or treatment, especially those that have a very high symptom load, adopting an interdisciplinary approach to rehabilitation and integrating this into the standard clinical pathway of cancer care may be desirable. An example of this is the integrated head and neck cancer rehabilitation program of the Netherlands Cancer Institute [31].

Concluding Remarks

To summarize, exercise can contribute to the health of individuals with cancer, but to successfully and safely employ exercise as an intervention, several prerequisites must be met. Physical, psychosocial, and environmental barriers may need to be addressed, and support of health-care professionals may be required accordingly. The more complex the health state, and the lower the ability of an individual to adapt to and self-manage the health problems he or she faces, the more need there is for involvement of health-care professionals and for a multidisciplinary approach to support exercise. All professionals working with individuals with cancer, both within and outside of the health-care system, need to maintain a broad perspective and escalate or de-escalate the level of support as needed. Viewing exercise through the lens of multidisciplinarity will ensure adequate exercise support, tailored to the needs of each individual with cancer, throughout all phases of cancer treatment and survivorship.

In order to attain a situation in which every individual with cancer receives the appropriate level of exercise support, the health-care infrastructure must be such that screening is standard, referral pathways are in place, and practical and financial barriers for patients are minimized. But most importantly, the when and how of multidisciplinary collaboration should be integrated firmly into the standard educational curricula of health-care professionals, as well as in those of exercise professionals training to work with individuals with cancer.

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Chapter 20
Policy and Reimbursement Considerations for Exercise Programming in Cancer

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Relevance of Policy and Reimbursement to Exercise Programming Among Cancer Survivors

Policy determines whether cancer survivors are able to access exercise programming. The decline in function that survivors experience is both stressful and demoralizing. Loss of function combined with uncertainties about the future, sometimes including the fear of death, manifest as feeling out of control. Exercise programming, when skillfully implemented, improves fatigue and function and offers an

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avenue through which a measure of control can be restored in addition to its extensive physiological benefits. The path to becoming an active participant in care rather than a passive recipient is thereby opened, empowering the survivor to contribute to their quality of life in a way that no one else on the care team can. The experience of improved function and energy through exercise promotes self-efficacy and helps ameliorate cancer-related distress. Policy and reimbursement that supports individualized exercise programming are therefore critical to improving a patient's well-being.

Policy informs each of the processes required for a cancer survivor to receive effective, individualized exercise programming. The range of processes is broad and includes screening for exercise needs; provider training and competency assessments; mandated on-site clinical exercise facilities, services, and specialists; and provision of patient education at critical points in the care trajectory. Perhaps most importantly, policy determines what exercise-programming services are reimbursed, how generously they are reimbursed, and for which diagnoses they are reimbursed.

While adoption is a vital first step, a policy's impact will be inevitably subject to the latitude that stakeholders are afforded in its enactment and the degree to which it is enforced. Policy can be highly prescriptive or discretionary, essentially left to stakeholder interpretation. Simply cataloguing public and private policy related to exercise programming, therefore, inadequately reflects which levers are enforced and influence care access and delivery. The extent and stringency of policy enforcement mediate its impact. The nature of oversight, therefore, deserves scrutiny equal to the specifics of written policy. If health-care providers and payers are not subject to consequences or incentives, policy outcomes generally fall short of their targets.

Reimbursement is the most frequent policy lever to used effect change. Reimbursement is uniquely relevant to cancer survivors since most are resource depleted, and up to 80% confront financial toxicity consequent to the cost of their care [1–3]. Further, as least initially, many survivors require some degree of human resource-intensive one-to-one care, e.g., physical therapy, in order to initiate effective exercise programming. Therefore, if the services are not covered or heavily subsidized, they become inaccessible for a majority of survivors. The extent of reimbursement is also critically important because if providers risk losing money, or a narrow profit margin, by providing exercise programming, they will not be motivated to do so.

This chapter offers an overview of public and private policy that influences the provision of exercise programming to cancer survivors. Policy relevant to the reimbursement of professionally delivered services is emphasized. The chapter's scope is restricted to policy related to exercise programming for secondary cancer prevention, promotion of general wellness, and mitigation of cancer late effects, as well as the provision of medical rehabilitation services to disease-free survivors. Research-related policy is not addressed.

Types of Policy Related to Exercise Programming

Policy related to reimbursement of specific services Policy originates from both the government and private sectors. The policy levers available to public and private groups differ, as does their capacity to enforce them. Payment levers can be uniquely effective, in part, by allowing health-care providers to profit. For example, generous facility and procedural fees have driven the growth of interventional pain management and other procedure-focused programs. Liberal reimbursement also motivates clinicians to seek the training and certifications required to provide lucrative services. Low reimbursement, in contrast, disincentivizes providers from developing or expanding service lines such as exercise programming for which generous reimbursement streams cannot be guaranteed. This contributes to limited patient access, long wait times, overburdened providers, abbreviated treatment intervals, and, ultimately, unsatisfactory patient experiences and outcomes.

Policy related to reimbursement of bundled services Reimbursement levers can penalize or reward providers through payment withholding or bonuses, respectively, contingent on the degree to which providers offer recommended, comprehensive services for complex and costly conditions. Cancer is a good example as certain treatments are lucrative, e.g., proton beam radiation, while others are less so, e.g., extended hospitalizations for treatment complications. Bundled care approaches are more comprehensive than policy targeting reimbursement for specific billing codes or the size of facility fees. The Oncology Care Model (OCM), a cancer-specific episode-based bundled payment initiative, required patient reported outcome (PRO) assessments of multiple domains including function. However, functional assessment was not mandated, and neither penalties nor incentives were directly linked to addressing functional deficits or providing exercise programming. Nonetheless, bundled care payment initiatives remain a popular means of ensuring the availability of effective, yet less generously reimbursed services.

Policy related to licensure Policy levers unrelated to reimbursement include the ability to revoke facility, institution, or practitioner licenses or to place requirements on the receipt of licensure. Revocation is an extreme measure that may deprive patients of vital local services, particularly in underserved areas, and is therefore seldom invoked outside of egregious breeches of clinical standards or professional etiquette. However, making licensure contingent on providers' achievement of specific competencies or institutions providing information/services to patients is a gentler and often effective approach. For example, in a recent effort to reduce opioid prescribing, the state of Florida required institutions and providers to educate patients about non-pharmacological pain care options.

Policy related to certification and accreditation Similar to the government initiatives, professional organizations may make certifications/accreditations contingent

on the achievement of professional competencies or the provision of specific services and education. However, private organizations have fewer resources than the government for monitoring and oversight. The strategy can be impactful when credentials are prestigious, linked to reimbursement, and/or useful for provider- and institution-level promotional activities. The Commission on Cancer (CoC) certification is an example. The COC mandates that its certified cancer centers ensure the availability of cancer rehabilitation services. This standard requires the availability of cancer rehabilitation professionals and lists physiatrists, physical therapists, occupational therapists, and speech language pathologists as typical cancer rehabilitation specialists. Types of services required include screening, diagnosis, and management of common impairments (including lymphedema), symptoms, and functional problems that cancer patients typically experience. The 2020 CoC specifications can be accessed at https://www.facs.org/-/media/files/quality-programs/cancer/coc/optimal_resources_for_cancer_care_2020_standards.ashx.

Policy related to mainstreaming Clinical specialty organizations enact policy designed to normalize the availability of services, such as exercise programming, by its members (both individuals and institutinos). Credentialing bodies, e.g., specialty boards, may normalize practices and services by including relevant content on examinations, which in turn drives the blueprints for study guides, text books, courses, etc. Specialty organizations can develop guidelines, conference content, white papers, etc., which may singly have limited impact, but collectively may become the basis for policy change.

Government Stakeholders in the Non-reimbursement Health-Care Policy Space

The powerful impact of reimbursement-related policy overshadows the vital role of federal, state, and municipal policies that influence whether cancer survivors integrate exercise in their lives during and after treatment. Policy at different levels of government advance or fail to advance philosophies regarding the importance of regular activity in everyday life. Governments can exert potent non-health-care reimbursement effects through public awareness campaigns, public education initiatives, zoning regulations, subsidies, tax exemptions, deployment of law enforcement resources to create safe exercise spaces, etc. The availability of parks; community exercise facilities; bike and jogging paths; evenly paved, well-lit sidewalks; and other sites where cancer survivors can engage in exercise are vital to sustaining the behaviors initiated through formal exercise programming. This chapter section examines culture, initiatives, and funding activities at the national, state, and municipal government levels that are supported by tax revenues.

Federal The Department of Health and Human Services (HHS), with a proposed 2020 budget of almost 1.3 trillion US dollars, is unequivocally the best funded

entity that enacts exercise-related policy. HHS is comprised of 11 operating divisions (Fig. 20.1), all of which have the potential to advance or hinder exercise-related initiatives. The Agency for Healthcare Research and Quality (AHRQ) and National Institutes of Health (NIH) focus principally on research and are therefore not considered in this chapter. However, AHRQ develops toolkits for health-care providers that advance guideline concordant care, some of which include exercise-related content such as "Linking Primary Care Patients to Local Resources for Better

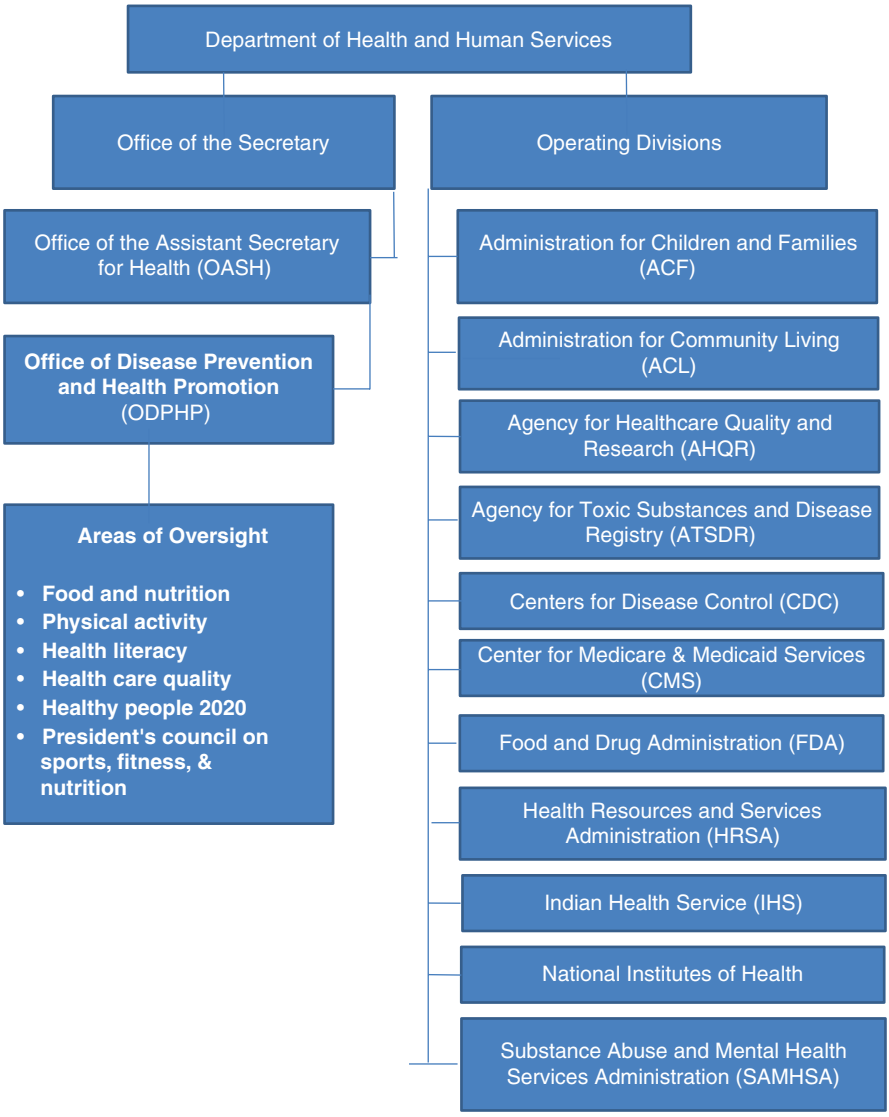

Fig. 20.1 Operating divisions of the Department of Health and Human Services

Management of Obesity." CMS and the Indian Health Service (IHS) also fall under the HHS umbrella but are principal payer/provider organizations and therefore referenced in the reimbursement policy section. The HHS operating divisions that most directly impact access to exercise programming are listed below.

Administration for Children and Families funds initiatives to revitalize communities which may include the creation of safe exercise spaces through community partnerships with their *Office of Community Services.* To date, no initiatives directly target cancer survivors.

Administration for Community Living provides grants to states and territories that support programs for older adults to promote healthy lifestyles and support healthy behaviors. They support *Can Do It!,* a program that helps schools offer physical fitness and nutrition education to students with disabilities.

Health Resources and Services Administration supports the training and distribution of health-care providers and additionally strives to improve health-care access to people who are vulnerable due to their geographic, economic, and/or medical status. The latter group, in theory, includes cancer survivors.

The Centers for Disease Control and Prevention website includes a "Cancer Home" with links to content for Staying Healthy During Cancer Treatment and Staying Healthy After Cancer Treatment. Both recommend healthy choices like "Being physically active," but do not offer more specific recommendations. Links are included to the National Cancer Institute's "Facing Forward: Life After Cancer Treatment" website (https://www.cancer.gov/publications/patient-education/facing-forward) and the American Cancer Society's "Be Healthy After Treatment" website (https://www.cancer.org/treatment/survivorship-during-and-after-treatment/be-healthy-after-treatment.html). These websites list activity/exercise along with many other preventative and wellness strategies, so a survivor must be intentional if they are to access the exercise-related content.

HHS also houses offices, including the Office of the Assistant Secretary for Health within which the *Office of Disease Prevention and Health Promotion* (ODPHP) is most directly charged with promoting physical activity to improve the health of all Americans. ODPHP formulates national health goals and objectives and participates in HHS activities for disease prevention, health education, and health promotion. ODPHP activities span prevention policy and clinical services, nutrition policy, health communication, and telehealth. OCPHP coordinates the US Preventive Services Task Force. Additionally, the OCPHP promotes access to health information by coordinating Federal health information resources through partnering with local channels, such as libraries, managing the web-based Federal consumer health information healthfinder (www.healthfinder.gov) and the National Health Information Center (NHIC).

ODPHP oversees the development, refinement, and dissemination of the Physical Activity Guidelines for Americans (https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf). Additional ODPHP exercise-related activities include their Move Your Way Campaign, National Youth Sports Strategy, and Healthy People 2020 physical activity objectives.

Although federal initiatives to promote exercise programming and increase physical activity are broad, few, if any, address the unique needs of cancer survivors.

State State initiatives to promote physical activity are heterogeneous and frequently parallel federal efforts. For example, California has developed a list of resources and tool kits for activity promotion (http://legacyplatform.libraryedge.org/sites/default/files/resources/healthtoolkit.pdf). Several high-yield targets for state activities have been proposed including the promotion of high-quality physical education for all students; community partnerships, especially with parks and recreation departments, to promote social support networks for physical activity, such as walking clubs and other group activities; and collaborations with employers to promote activity among adults [4]. Similar to federal initiatives, state-based exercise programming activities are public health directed and commonly target obesity. Per a searchable CDC dataset that contains nutrition, physical activity, and obesity policy data for 50 US states and DC from 2001 to 2017, only one state-level policy directly addresses exercise/physical activity among cancer survivors (https://www.cdc.gov/nccdphp/dnpao/division-information/policy/index.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fnccdphp%2Fdnpao%2Fdivision-information%2Fpolicy%2Fphysicalactivity.htm).

Municipal Municipalities are diverse with respect to their geography, demographics, and resources, as well as their cultures for initiating and reporting exercise promotion policy. The inconsistency of this reporting hampers efforts to identify consistent patterns or trends. Nonetheless, a Utah-based study found that a small proportion of municipal staff were employees responsible for physical activity policies, and that high growth cities reported more ordinances encouraging physical activity [5]. A more recent report from Hawaii noted that the most populous county, Honolulu, had the most policies in place, although discrepancies existed between reported and written policies [6]. Additionally, among city officials from eight different states, those who resided in the city and used facilities were more likely to engage in land use policies supportive of active living [7]. Problems have been noted with audit tools designed to assess compliance with ordinances for bicyclist and pedestrian access. Few have been rigorously tested, and a general lack of data has been attributed to budgetary constraints [8]. Similar to Federal and State policy, the few discoverable municipal policies related to exercise programming do not target population subgroups distinguished by clinical characteristics, including cancer survivors.

Commercial and Organizational Stakeholders in the Nonreimbursement Health-Care Policy Space

Diverse private stakeholder groups engage in activities designed to promote exercise behaviors among cancer survivors. These stakeholders span professional clinical societies, international organizations, and patient advocacy groups. While many

groups encourage exercise and outline its health benefits, few specify the type, intensity, and duration of physical activity cancer survivors should perform to realize specific physical benefits. Most exercise recommendations are geared to the general population for primary prevention, and the recommended duration and intensity are fairly generic. Table 20.1 provides an overview of the exercise-related policy, as well as the recommendations of several national and international organizations. The table is not comprehensive, but it offers a general overview of current organizations and a representative sample of exercise programming-related policy activities in the commercial and organizational space.

The World Health Organization (WHO) is more similar to US federal agencies; however, it targets countries, rather than states, to advance its agenda. Specifically, the WHO has a four-tiered policy to realize their *Global Action Plan on Physical Activity 2018–2030* that includes implementing behavior-changing advertising campaigns to alter social norms, promoting safe infrastructure and public open spaces to support physical activity, ensuring access to programs and services, and strengthening advocacy and leadership systems for coordinated policy implementation. LIVESTRONG Foundation, in contrast, engages in patient-oriented activities and offers exercise programming. LIVESTRONG has several programs for cancer survivors, including a navigation program to help with the physical and emotional adjustments after cancer, a fertility program providing education and financial support, a K-12 school program to help educators share information about cancer, and a collaboration with the YMCA to promote the importance of physical activity after a cancer diagnosis. Since 2007, the LIVESTRONG Foundation and the National YMCA have collaborated to develop an affordable 12-week program inside YMCA facilities for cancer survivors to have readily accessible community activities from a certified fitness instructor.

The American Cancer Society provides resources directed to both patients and clinicians; the former in support and education, but not exercise programming, and the latter predominantly in grant support.

Many clinical professional organizations engage in diverse activities to support the exercise programming provided to cancer survivors by their membership. Some offer credentialing programs that enable motivated members to gain the knowledge and clinical skills needed to provide effective, individualized exercise programming. The American College of Sports Medicine has been the most active in promoting exercise programming for the primary and secondary prevention of diseases including cancer. The ACSM initiatives include “Exercise is Medicine,” a program to promote physical activity into treatment plans by primary care physicians; “Moving Through Cancer,” a program specifically designed to take actions toward making exercise standard practice for people living with and beyond cancer; and the “ActivEarth” program to promote active transportation such as walking and bicycling in the community, and a detailed infographic to illustrate expert recommendations on exercise in cancer (https://www.acsm.org/read-research/newsroom/news-releases/news-detail/2019/10/16/expert-panel-cancer-treatment-plans-should-include-tailored-exercise-prescriptions.)

The American Society of Clinical Oncology (ASCO) offers online resources for patients including ASCO Connection, their online journal, and professional

Table 20.1 Characteristics and scope of activities among stakeholder groups in the nonreimbursement policy space related to exercise programming among cancer survivors

	Description	Membership	Activities							
			Patient programs	Guidelines/ recommend-ations	Whitepaper/ position statement	Education	Special Interest Group	Funding	Promotional materials	Certification/ accreditation
International										
World Health Organization (WHO)	Specialized agency of the United Nations established in 1948 that is concerned with international public health	Countries		X	X	X		X	X	
Patient										
LIVESTRONG	Patient advocacy organization founded in 1997 to improve the lives of people affected by cancer	Supported community programs	X			X		X		
Hybrid Patient/Clinician										
American Cancer Society (ACS)				X	X	X		X	X	

(continued)

Table 20.1 (continued)

	Description	Membership	Activities							
			Patient programs	Guidelines/ recommend-ations	Whitepaper/ position statement	Education	Special Interest Group	Funding	Promotional materials	Certification/ accreditation
Professional clinician organizations										
American Academy of Physical Medicine and Rehabilitation (AAPM&R)	Founded in 1938 to lead the advancement of physiatry's impact	~ 9K PM&R* physicians				X	X			
American College of Sports Medicine (ACSM)	Founded in 1954 to advance and integrate research on exercise science and sports medicine.	Sports medicine professionals with over 50K members from 90 countries,		X	X	X	X		X	X
The American Society of Clinical Oncology (ASCO)	Founded in 1964 to improve the care of people with cancer	45K oncology clinical professionals, and researchers from over 150 countries				X				
The American Physical Therapy Association (APTA)	Founded in 1921 to advance the profession of physical therapy to improve the health of society	~100K PTs, PTAs, and PT students				X	X			X

The American Occupational Therapy Association (AOTA)	Founded 1917 to represent OTs and improve the quality of OT services	~60K OTs and OT students					X			
American Congress of Rehabilitation Medicine (ACRM)	Founded in 1923 to improve the lives of disabled individuals through interdisciplinary rehabilitation research	>3K rehabilitation service providers and researchers from more than 65 countries				X	X			
Standard setting										
Commission on Cancer (CoC)	Developed in 1922 to establish standards for cancer treatment by the American College of Surgeons (ACOS)	>1500 CoC-accredited cancer treatment sites								X

networking website. Another of ASCO's online resources is the Cancer.Net website, which lists exercise tips during cancer treatment and physical activity tips for survivors in their survivorship and has a healthy living section. Of note, a few, if any, of these stakeholder groups engage in oversight activities to ensure the quality and safety of exercise programming delivered to patients or to encourage clinicians to systematically integrate exercise programming in cancer care. That said, the Moving Through Cancer initiative of the American College of Sports Medicine plans to address these issues in coming years, pending funding.

The American Physical Therapy Association (APTA) has been among the most active clinical professional organization in establishing certifications and training opportunities to promote the delivery of evidence-based exercise programming to cancer survivors. In 2016, the APTA House of Delegates approved board certification in oncology, and the first oncology specialist certification examination was offered in the spring of 2019. Representing the growing cancer interests in physical therapy is their own Academy of Oncologic Physical Therapy. They have cancer special interest groups in lymphatics, pediatrics, hospice/palliative care, and falls. They promote academy courses for exercise training guidelines and on how to assess the exercise capacity of survivors and how to track changes in fitness in this population.

The American College of Surgeons' established Commission on Cancer (CoC) is unique in its efforts to promote cancer treatment standards. To qualify as a CoC-accredited cancer treatment site, facilities must demonstrate that they have met certain standards and offer a range of cancer-care services including lifelong follow-up. The Optimal Resources for Cancer Care: 2020 Standards is a 92-page document freely available online. Part of eligibility requirements for certification includes rehabilitation services that include "physical activity recommendations during and after treatment." Physical activity is mentioned in 2 other standards, the first requiring a survivorship program and the second requiring an annual cancer prevention event.

In summary, there are many national and international non-government organizations that offer opinions on physical activity and its health benefits, but few have developed effective strategies to promote physical activity among cancer survivors. Many professional clinical groups lack a formal position on physical activity and cancer, yet implicitly endorse physical activity on their websites and promotional materials. However, only the CoC explicitly requires accredited institutions to ensure the availability of rehabilitation services to their patients, and even the CoC is silent with respect to the provision of general exercise programming.

Government Stakeholders in the Reimbursement/Coverage Health-Care Policy Space

The largest and the most impactful players in reimbursement for exercise programming are Medicare at the national level and Medicaid at the state level. As of 2019, there are over 65 million enrollees in Medicaid and over 59 million enrollees in Medicare/Medicare Advantage [9, 10]. By comparison, this is more enrollees than

the largest three private health insurance companies combined (111 million enrollees total in UnitedHealth, Anthem, and Aetna) highlighting the importance of national and state policy in delivering rehabilitation and exercise programming services to patients with cancer. The remainder of this section will discuss the coverage benefits and limitations of Medicare, Medicare Advantage Plans, Medicaid, and CHIP.

Medicare (also called Fee-for-Service Medicare) is the national insurance program providing health insurance for Americans aged over 65 and some citizens under age 65 with disability status. It is divided into parts A, B, C, and D with part A covering hospital insurance, part B covering medical insurance, part C covering Medicare Advantage Plans, and part D covering prescription drugs. Part A covers in-patient rehabilitation in addition to rehabilitation in a skilled nursing facility (subacute rehabilitation). Medicare will cover up to 100 days of subacute rehabilitation provided that certain criteria indicating medical necessity are met including a preceding 3-day in-patient hospital day, the need for daily skilled care as determined by a physician, and the need for skilled care due to a hospital-related medical condition. There is a co-pay of $176 per day following day 20 [11]. The 100-day clock is reset if a beneficiary goes at least 60 days without receiving a facility-based care, that is, in-patient care in a hospital or care at a post-acute care facility.

Part B of Medicare covers outpatient rehabilitation services including physical therapy, occupational therapy, and speech language pathology. Fee-for-Service Medicare does not currently reimburse exercise programming provided by exercise physiologists, personal trainers, or instructors of alternative exercise traditions such as Pilates, yoga, and Tai Chi. Gym memberships or fitness programs may be part of the extra coverage offered by some Medicare Advantage Plans. US governmental coverage differs from other countries. in that patients' out-of-pocket costs for exercise programming may be substantial despite Medicare's PT and OT coverage. As of 2019, after patients pay a deductible of $185, Medicare covers 80% of PT and OT services, while beneficiaries will cover the remaining 20% as a coinsurance payment [12]. Prior to 2019, there were "therapy caps" whereby Medicare would only cover up to $2040 for occupational therapy and an additional $2040 for combined physical therapy and speech language pathology (SLP) services. At approximately $100 per session of therapy, this amounted to 20 visits for OT and a combined 20 visits for PT/SLP per benefit year. In 2018, the government passed the Bipartisan Budget Act of 2018 which removed these caps. As of 2019, the $2040 mark is now the threshold, which if exceeded, providers must indicate that further therapy is medically necessary [13]. For example, if a patient uses $2000 worth of physical therapy benefits for chronic back pain but then develops poor balance secondary to chemotherapy-induced peripheral neuropathy in the same benefit year, further therapy would be medically necessary.

To protect the Medicare trust fund against inappropriate payments, there is a medical review for services that exceed $3000 [13]. For instance, it would not be appropriate to write ongoing occupational therapy prescriptions for manual lymphatic drainage to address stable lymphedema controlled with garments and exercise. Such a claim would be appropriately subject to review. In a medical review,

there is collection of information and a clinical review of medical records by Medicare Contractors to ensure that payment is made only for services that meet all Medicare coverage, coding, and medical necessity requirements. If a review occurs and adequate criteria for services are not met, it is possible that Medicare could seek payment recovery/recoupment for services already rendered. Although there is technically no limit on the dollar amount spent on exercise programming, there is also no limit on the out-of-pocket costs for the beneficiary. Co-pays for therapy visits, in addition to substantial deductibles, can quickly add up and pose a significant barrier for patients in need of treatment, and alternative forms of coverage should be explored. For beneficiaries requiring assistance for costs incurred with Fee-for-Service Medicare like co-pays and deductibles, there is Medicare Supplemental Insurance also known as Medigap. Medigap plans are sold by private insurance companies and require payment of premiums in addition to the premium paid for Fee-for-Service Medicare. Because there is no cap to a beneficiary's out-of-pocket expenses with Fee-for-Service Medicare, supplemental Medigap plans may be an appropriate option for individuals with higher expected costs.

Medicare Advantage Plans is another name for part C of Medicare in which Medicare benefits (parts A, B, and usually part D) are provided through a private insurance company. These companies are approved by Medicare, and Medicare pays them directly to deliver the benefits [14]. In addition to consolidating services under a single plan, Medicare Advantage Plans have an annual out-of-pocket maximum opposed to Fee-for-Service Medicare and sometimes offer extra services like vision and dental at low to sometimes zero extra premium costs making it an attractive option for patients with a chronic and serious illness like cancer. Enrollment in Medicare Advantage Plans has nearly doubled in the past 10 years from 10.5 million enrollees in 2009 to 22 million enrollees in 2019 and will likely continue to grow over the next 10 years [15]. Medicare Advantage Plans are required to cover at least the same benefits that Fee-for-Service Medicare does including services for PT and OT. The exact limitations and co-payments required for PT and OT services vary depending on the individual insurance company and plan. Similarly, Medicare Advantage Plans coverage of exercise programming provided by exercise physiologists and personal trainers varies across plans. However, since the scope of Medicare Advantage Plans coverage rarely exceeds that of Fee-for-Service Medicare, more permissive plans are uncommon.

In contrast to Medicare and Medicare Advantage Plans, Medicaid is an insurance program for the American families with low income, qualified women and children, and individuals who receive supplemental security income. As with Medicare, Medicaid also covers in-patient rehabilitation and rehabilitation services in skilled nursing facilities although there is no 100-day limitation. Under federal guidelines, there are certain mandatory benefits which state Medicaid programs must provide including inpatient hospital services, nursing facility services, and home health services. Other services including PT, OT, and SLP are considered optional benefits which states may or may not include within their own individual Medicaid policies [16]. Information on Medicaid benefits in 2018 from the Henry J. Kaiser Family Foundation indicates that currently 39 states and the District of Columbia provide the optional PT benefit under their Medicaid programs [17]. In general, most states that provide the benefit will allow for somewhere between 15 and 20 visits per year.

Some states will require a small co-payment for each visit, and a few states will require prior authorization [17].

The Children's Health Insurance Program (CHIP) is an insurance program providing health insurance to children up to the age of 19 in families that have low incomes, but not low enough to qualify for Medicaid. Similar to Medicaid, it is administered at the state level within federal guidelines. As with Medicaid, states have the option of whether or not to provide PT and OT benefits. Most states do cover them, and providers should refer to their state's provider manuals for details. Another important source of government-funded exercise programming comes from the Individuals with Disabilities Education Act (IDEA). The purpose of IDEA, which was renamed and reauthorized in 1990, is to provide children with disabilities with free and appropriate public education. PT and OT services are covered in part B (assistance for education) of IDEA and children affected either directly or indirectly from cancer diagnoses may be eligible. Providers can contact the school's principal or director of special education to get eligible children the benefits they may be entitled to.

Private Stakeholders in the Reimbursement or Coverage Health-Care Policy Space

Commercial health insurance in the United States is insurance administered by non-government entities. Employer-based insurance is the most common type of commercial health insurance and the most common type of overall coverage in the United States [18]. According to the US Census Bureau's Health Insurance Coverage in the United States 2017 report, 294 million individuals or 91.2% of the population had health insurance and 67.7% received coverage through commercial payers [18]. Many of the commercial payers sell tiered plans to small and large businesses, plans to individuals on the government's Health Insurance Marketplace, and Medicare Advantage Plans. In 2016, as a result of mergers and acquisitions, it was estimated that five companies covered 43% of the total insured population [19]. Large commercial payers in the United States include Aetna®, Anthem®/Blue Cross Blue Shield Association® (BCBS), Cigna®, Humana®, and UnitedHealthcare®. In selected states, BCBS operates single-state licenses and is part of member organizations in others [20, 21]. There are also private, publicly traded companies which administer government-sponsored programs, such as, Medicaid and Medicare. Examples of these payers include Centene®, Magellan Health, Molina®, and WellCare® (now part of Centene). The health insurance companies mentioned in this section do not represent all commercial payers in the United States and were selected to illustrate the spectrum of services potentially available to patients. Information about coverage was obtained via the companys' websites.

Many individuals with cancer depend on private health insurance for medical coverage. A study by Thorpe et al. utilizing Medical Expenditure Panel Survey (MEPS) data from 1996 to 1999 reported that 33% of all cancer patients had private insurance at the time of the first cancer event. Among individuals under the age of 65 years, 70% had private insurance [22]. Notably, according to the

MEPS [23], private insurance covered 44% of the $87.8 billion US total expenditure for the cancer costs in 2014 [23]. The commercial health insurance market in the United States represents a formidable stakeholder in the health-care industry.

Similar to the heterogeneity noted among state Medicaid plan with respect to PT and OT coverage, commercial payers' coverage of exercise programming is highly variable. Virtually all reimburse PT and OT services; however preauthorization requirements, number of sessions and diagnoses covered, and co-payments range widely. Because commercial payers compete to for employer contracts, they may be more responsive to patient preferences than federal payers. Therefore, most offer access to exercise programming services outside of PT and OT. Commercial exercise-programming benefits are, for the most part, condition agnostic and do not afford unique programming opportunities to cancer survivors.

Commercial Payer-provided Wellness Programs Health-care providers may leverage resources from the already established programs provided by commercial payers to promote physical exercise participation. Commercial payers offer dedicated resources to encourage healthy lifestyle practices. These vary across programs, but often include biometric and other assessments, discounted gym memberships, subsidized purchase of exercise equipment, and access to wellness coaching. Additionally, nearly all companies have health education informational sheets and/or videos. More recently, many commercial providers have offered platform-based activity promotion programs with financial and other incentives. Table 20.2 describes programs offered by some of the largest payers which may be accessible to cancer survivors.

Table 20.2 Wellness programs offers by commercial insurance plans

Payor	Program name	Program description and components
Commercial plans		
Aetna®	Get Active! SM program	An online program connected to an activity tracker that presents challenges and rewards to participants
	Attain by Aetna®	A direct-to-consumer smartphone app-based interface with a points-based rewards program. Points are redeemed for gift cards or activity monitors such as Apple watches
Anthem®/Blue Cross Blue Shield®	Be Well SHBP	A platform offers a point-based rewards system and encompasses a health risk assessment, daily tracking, a library with personalized health education and a community interface where members participate in challenges
Cigna®	Healthy Rewards	Discounts towards fitness-related purchases and uses a tool to sync physical activity data and to extract data from exercise equipment
	Just alk 10,000 Steps-a- Day	An 8-week program that includes a pedometer, motivational messages, and a walking handbook (10,000 steps)

Table 20.2 (continued)

Payor	Program name	Program description and components
	Coach by Cigna	Free app with unrestricted access (not just Cigna beneficiaries) easy to follow programs and daily to-do lists and messaging from a team of health coaches
Humana®.	Go365 Program Wellness & Rewards Program	A health assessment that leads participants to a personalized interactive platform that centers around a points-based rewards system that may be used towards wellness and entertainment goods. The interface includes smartphone app-based services, such as, called Fitbit Coach and the DailyBurn, which provide coaching and has a collection of work-out videos
UnitedHealthcare®	Simply Engage®	An assessment that includes a survey and biometrics analysis which affords access to a "Gym Check-In program and an interactive platform called Rally.® The Rally® interface includes a, physical activity monitoring, online communities, and a rewards-based platform
	Sweat Equity Program	Reimburses $200 if a participant attends 50 cardio-based exercise sessions over a period of 6 months
	United Healthcare Motion	A platform that enables individuals link activity monitoring devices and work to meet FIT goals to receive financial incentives
Magellan Health	CaféWell®	An online interface that offers credit toward monthly medical plan payments. The program includes a risk screen, a biometrics assessment, an online coaching, a physical activity monitoring, and an online community platform. The program also covers five nutrition visits annually
Medicare Advantage Plans		
Aetna®, Blue Cross Blue Shield® and Humana® plans	Silver Sneakers®	An online platform with educational materials, access to group exercise classes, and provides complimentary fitness center membership at contracted locations
Cigna®	Silver&Fit®.	Provides fitness center memberships, home fitness options, and rewards for wearing activity monitors

The reported outcomes of payer-provided wellness programs are encouraging. Go365® released five-year outcomes from 2011 to 2016. It compared findings from years 1–2 (baseline) to years 3–5 of approximately 10,600 Humana® employees. At baseline, 36% participants exercised 150 minutes or more per week, and this increased to 62% at year 5. High program users had fewer total allowed claim costs for lifestyle-related chronic conditions, fewer hospital admissions, and fewer "unhealthy" work days. UnitedHealthcare's Motion program reported that the 37,000 participants walked an average of 12,000 steps daily and about 45–65% of

the eligible members signed up for the program. A more rigorously designed cluster-randomized trial of 20 workplace wellness programs and 140 control worksites, with approximately 4000 participants in each group, found a higher rate of exercise engagement but no difference in health-care utilization in the intervention group [24]. Though promising, these results may not accurately reflect the experiences of cancer survivors participating in wellness programs.

Insights from Successful Exercise Programming for Cancer Survivors in Germany

Germany has the most broadly implemented and accessible exercise programs for cancer survivors in the world. Therefore, the chapter includes an overview of German policies and reimbursement related exercise programming in cancer to afford insight into this case of "positive deviance." Germany has a network of various medical and social support and counseling services, where former cancer patients can find help. Part of this network is the German Cancer Information Service, which provides cancer information for patients, their families, the general public, and health-care professionals. A team of physicians answer all the cancer-related questions.

As the largest network of oncology experts in Germany, the German Cancer Society not only deals with questions concerning cancer care but also provides expert opinion on health-policy issues in various committees, discussions, and opinion forms. In collaboration with the German Cancer Aid and the Association of German Tumor Centers, the German Cancer Society is the cofounder of the German National Cancer Plan, which was launched in 2008 by the Federal Ministry of Health.

The National Cancer Plan initially focused on the following fields:

- Further development of cancer screening
- Further improvement in the structural aspects of oncology care and quality assurance
- Ensuring effective oncological treatment (initial focus on drug therapy)
- Strengthening patient orientation in cancer care

The latest campaign "Keep the ball rolling - Exercise lowers your risk of cancer" is a joint project with soccer player Lukas Podolski, the German Football Association (DFB), and the German Cancer Aid to improve physical fitness among children and adolescents.

Rehabilitation Program Provided by the Pension Insurance

Three-week inpatient programs paid by pension insurance provide a multidimensional and multidisciplinary cancer rehabilitation approach, extensive sport, and exercise programs with health education included.

Exercise Offerings for Cancer Patients

Large cancer centers offer patients the opportunity to obtain advice on sport and exercise. Many offer exercise programs as part of aftercare or carry out scientific studies on exercise and sport after cancer. Rehabilitation exercise groups in cancer aftercare are offered by the German Disabled Sports Association. General sport offerings in the region can be found on the website of the German Olympic Sports Confederation.

Rehabilitation Sports Groups

Sports groups for people with cancer are offered as rehabilitation sports in rehabilitation sports groups via the "Deutscher Behindertensportverband (DBS)." Under www.dbs-npc.de/sportentwicklung-rehabilitationssportgruppen-in-deutschland.html, affected and interested ones can search for rehabilitation sport groups.

Movement offerings for cancer survivors have existed in Germany for a long time: the first cancer survivorship sports groups were established in 1981. At the same time and independent of each other, the Landessportbund Nordrhein-Westfalen and the German Sports University Cologne founded sports groups for women after breast cancer. In Cologne, scientists carried out initial studies on exercise therapy in oncology in order to clarify the effects of physical activity in rehabilitation on breast cancer patients. There are now around 1000 rehabilitation sports groups throughout Germany, which is unique in the world. Since 1991, all training supervisors in Germany have been subject to a uniform training program via the regional and disabled sports federations.

Health insurance funds support participation in a rehabilitation sports group for 18 months. Each affected health insurance patient is initially prescribed 50 exercise units (at least 45 minutes each) of rehabilitation sport in a sports club certified by the Landessportbund or the "Behindertensportverband." The number of units can be extended individually. The rehabilitation sports groups meet regularly, but medical supervision is not necessary.

Disease Management Program: DMP

Since 2001, breast cancer patients have had the opportunity to participate in targeted treatment programs. The term Disease Management Program (DMP) stands for controlled and careful treatment planning as well as the alignment of diagnostic and therapeutic offers with current quality requirements. The exercise programs developed and evaluated to date have already been made available to all statutory health insurance funds as supplementary programs to DMP patient training courses. Further exercise programs are under development. The provision of such programs is to be expanded across the board in the coming years. This means that all

participating physicians, hospitals, and other service providers work closely together and coordinate decisions better. The patient participates in exercise programs and receives comprehensive information.

OnkoAktiv Network

The OnkoAktiv network (www.netzwerk-onkoaktiv.de) connects cancer patients to oncology-trained and certified exercise facilities near patients' homes in Germany. Further, OnkoAktiv offers a structured evidenced-based counselling process involving oncology health care and exercise professionals.

Financing: Who Bears the Costs?

Depending on the individual insurance situation and the background of the rehabilitation measures, the rehabilitation costs are borne by the statutory pension insurance, the federal and state governments for civil servants, soldiers and other occupational groups entitled to aid, the statutory health insurance, possibly also the statutory accident insurance (if the tumor disease was recognized as occupational), or the private health insurance. Doctors can prescribe survivorship training in cancer aftercare for patients. The statutory health insurances then contribute to the costs at least temporarily. Rehabilitation sport is a supplementary service on the part of the payers and, in contrast to physiotherapy, cannot be billed within the scope of medical services.

Examples of Effective Policy-Based Advocacy to Increase Patient's Access to Exercise and Rehabilitation Services

Cardiac rehabilitation is often hailed as a success in the United States and presented as a foil to the general under-development of exercise programming for cancer survivors. However, in reality cardiac rehabilitation has also struggled, and lack of reimbursement remains the greatest barrier to its broad disemination [25]. The "International Council of Cardiovascular Prevention and Rehabilitation" (ICCPR) founded in 2011 [26] used successful tactics to overcome this barrier. This society links rehabilitation with prevention since modifiable risk factors are well established in cardiac disease. ICCPR has developed a global certification program for cardiac rehabilitation. Due to these efforts, 111 countries currently have cardiac rehabilitation [27]. American and British CR societies have also launched their own certificate programs and provide examples of successful achievements in both

insurance-based and government-funded programs, respectively [27]. Evidence-based campaigns and advocacy for the inclusion of standards of delivery in the national guidelines in the United Kingdom had a large impact. This resulted in improved referrals and a national commissioning guide and tool kit to fund cardiac rehabilitation [25]. Trends include moving away from expensive hospital-based settings and allowing for more individualized programs [28].

Such efforts may not be possible in low-income countries. Suggestions for low-income countries include unsupervised exercise or exercise in a community (nonhospital) setting [29]. The Mayo Clinic found a way to train leaders in underserved countries in the field of cardiac rehabilitation in Latin America. [28] This increased visibility and publications. Collaboration between academic groups and health and economic government departments is highly recommended to improve access for all. [28]

The American Association of Cardiovascular and Pulmonary Rehabilitation (AACPR) founded in 1985 developed appropriate outcome measures and established evidence to support both the efficacy and cost-effectiveness of cardiac rehabilitation in the United States [25]. This resulted in the distribution of performance measures, insurance coverage by the state health plans, and the inclusion of heart failure under indications [25].

As a consequence of effective advocacy, cardiac and pulmonary rehabilitation programs are currently approved by Medicare, and most commercial payers, for specific cardiac and pulmonary conditions. In addition to proving underlying pathology, patients must demonstrate symptomatic need and the ability to participate in the program. These programs are multidisciplinary but emphasize supervised physical exercise. Because cancer survivors are at risk of developing cardiopulmonary dysfunction, they may be eligible for and benefit from cardiac rehabilitation. Pulmonary rehabilitation may be easier for some survivors to access. For instance, Aetna® includes conditions such as radiation pneumonitis, scoliosis, and pulmonary fibrosis under the umbrella diagnosis of chronic pulmonary disease (Aetna Pulm Rehab). Anthem® and its BCBS subsidiaries also include “stable lung cancer” as a qualifying diagnosis for pulmonary rehabilitation [30].

Lymphedema

Advocacy has been notably effective for one cancer-related impairment, lymphedema. As early as 1998, Medicare covered 2 weeks of complete decongestive physiotherapy (CDP) in Florida due to medical activism by patients, health-care providers, and the National Lymphedema Network (founded in 1988) [31]. By 2009, three states had passed legislation to demand adequate insurance coverage for lymphedema treatment and diagnosis [32]. HB-1737 of Virginia (2003), AB-213 of California (2007), and S.0896 of Massachusetts (2009) require that insurers provide coverage for CDP, supplies, equipment, education, and self-management. The California bill also demands coverage for physician diagnosis and plan of care.

Medicare coverage varies by state, and efforts are underway to ensure that all patients have access to lymphedema diagnosis and treatment, both to improve outcomes and decrease cost. Currently, the Lymphedema Treatment Act is an active bill in the 2019–2020 Congress to change Medicare law to mandate coverage for lymphedema supplies and equipment throughout the United States, regardless of the cause of lymphedema. As of fall of 2019, the bill passed in the House and awaits presentation in the Senate. Many societies are involved in the support of this bill such as the National Lymphedema Network, the first to advocate in this domain. Others include the American Medical Association, American Academy of Physical Medicine and Rehabilitation, American Cancer Society; Oncology Nursing Society; American Occupational Therapy Association; American Physical Therapy Association; Wound, Ostomy and Continence Nurses Society™; National Patient Advocate Foundation; LIVESTRONG; Colon Cancer Alliance; Susan G. Komen; Ovarian Cancer National Alliance; American Lymphedema Framework Project; Lymphatic Education & Research Network; and Lymphology Association of North America.

Conclusion

Neither government nor commercial reimbursement policies offer cancer survivors in the United States access to evidence-based, high-quality exercise programming. Successes achieved in Germany, as well as other European countries, and by focused condition-specific efforts, e.g., lymphedema, in the United States offer potential roadmaps for advancing the critical need for fitness and exercise guidance to the burgeoning population of increasingly elderly cancer survivors.

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Chapter 21
Shaping the Future of Exercise Oncology

Kathryn H. Schmitz

A review of PubMed will reveal that the field of exercise oncology has grown exponentially in the past decade. As a result, the American College of Sports Medicine convened a second roundtable, an international, multidisciplinary roundtable on exercise and cancer prevention and control. The resulting papers, published in Fall 2019, could not contain all of the cutting edge science presented at the meeting. This volume is one attempt to bring to light the remarkable exercise oncology research completed over the recent past. The roundtable activities spawned a new multidisciplinary initiative, called Moving Through Cancer (exerciseismedicine.org/movingthroughcancer). The mission of this new initiative is that all people living with and beyond cancer will be appropriately assessed, advised, and referred to high-quality exercise programming from diagnosis and through the balance of life. The expert panel that guides this initiative believes that we have reached the tipping point with regard to the evidence base: we know enough, and now the question is not *whether* we should make exercise standard during and after cancer, but *how*. That said, there is more work to do in the science connecting exercise and cancer. In this text, we have reviewed the most recent evidence. The field of exercise oncology might be said to have grown to have multiple subsections: prevention (primary and secondary), mechanisms, improvements in cancer-related health outcomes during and after treatment, and treatment efficacy/tolerance, as well as the systemic issues in translating the evidence base into clinical and community practice (behavioral, logistical, and policy issues). Review of the current state of the evidence allows us to point toward the future of the field. Below, we review the pressing issues that currently remain in exercise oncology.

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Exercise for Cancer Prevention

The authors of Chaps. 2 and 3 present strong evidence for a preventive effect of exercise, particularly for the more common cancer sites, such as colon, endometrial, and breast cancers. More recent data suggest decreased risk of esophageal, liver, bladder, gastric, and renal cancers for the most physically active. It also seems that it will be possible to discern the relationship of exercise with rare cancers in the foreseeable future. Dose response questions remain as well (e.g., how much exercise is enough to reduce risk by how much). Questions surrounding the role of sedentary behavior and cancer prevention remain to be answered, requiring ongoing surveillance and, in all likelihood, pooling of multiple large cohorts. It is possible that transdisciplinary teams of preclinical and epidemiologic scientists could move this agenda forward more quickly than either group alone.

Similar prevention questions remain regarding exercise and cancer survivorship, particularly regarding less common cancers, timing of exercise, and the role of sedentary behavior. There continue to be unanswered questions regarding the role of resistance exercise and cancer prevention and survival, in part because we do not measure resistance exercise well in large epidemiologic cohort studies.

The mechanisms supported by strong evidence to link exercise and cancer prevention include alterations of tumor vasculature, immune responses to cancer, and tumor cell intrinsic and extrinsic characteristics. The effects of exercise on the tumor microenvironment remain an area of active investigation. The vast majority of the research on these mechanisms is from preclinical models. There is a need to translate this work into the human model – it cannot be assumed that results we see in the rodent will hold true in humans. Thus far, there has been little human research that has examined the effects of exercise on body tissues in which cancer occurs, to examine effects at the tissue level. Further, there are scant preclinical models to examine effects of exercise on cancer recurrence. Development of additional model systems for this purpose would assist the field in important ways. As with primary prevention, transdisciplinary work that combines the best efforts of human clinical trials and rodent experiments might prove expeditious.

Exercise from Diagnosis to the End of Treatment

Prehabilitation is an area that has gained tremendous momentum over the past decade. There are sufficient data in colorectal and lung cancer that a multimodal program of exercise, diet, and other prehabilitative services results in improved disease-specific endpoints such as cancer therapy completion, as well as surgical and functional outcomes. Further, there is growing consensus that exercise should be applied postoperatively, as part of an Enhanced Recovery After Surgery (ERAS) program. The evidence base for the use of ERAS within surgical patients of all kinds is quite strong, and the authors of Chap. 7 conclude that “exercise should be a mainstay of the postoperative management of oncologic patients.” That said, there

are numerous remaining questions regarding the dose and timing of the interventions for best outcomes, as well as expanding trials to additional tumor sites. Clarification of dosing and combinations of therapies might be ripe territory for preclinical research as well. The evidence base in prostate, breast, and hematologic malignancies is developing. Further, for prehabilitation and all other exercise interventions after diagnosis, the logistics, behavioral, and policy issues remain to be addressed. It is notable that most of the chapters in this book mention something about the behavioral, logistical, or policy issues facing exercise oncology as a field.

With the publication of the ACSM Roundtable documents in fall 2019, we see that the evidence base supports a specific FITT (frequency, intensity, time, and type) exercise prescription to address eight specific cancer treatment-related symptoms and side effects, including fatigue, sleep, quality of life, function, depression, anxiety, bone health, and lymphedema. That said, the expert panel that completed this review (led by Dr. Campbell, lead author of Chap. 8) identified that there was insufficient evidence to conclude that exercise would have a significant effect on cognitive function, cardiotoxicity, chemotherapy-induced peripheral neuropathy, falls, nausea, pain, sexual function, or treatment tolerance. There has long been sufficient evidence to document the safety of exercise during chemotherapy, as well as the benefits of exercise during chemotherapy on cardiovascular fitness and muscular strength. By contrast, there is relatively little research on the topic of exercise concurrent to immunotherapy. This is a particularly promising area for future research, given that immunotherapy is being prescribed more frequently.

The safety and efficacy of exercise during radiotherapy have been less well studied than for infusion therapy. There are trials in breast cancer, prostate cancer, and head and neck cancer, which have examined the effects on symptom-based outcomes, such as fatigue and upper limb function. The author of Chap. 9 (Dr. Wiskemann) particularly calls out for additional research in the area of exercise during palliative radiotherapy, particularly to assess whether exercise and muscular stabilization rather than activity restriction may net better outcomes.

Questions regarding the role of exercise for improving treatment efficacy or tolerance/completion are largely unsettled at this time, despite multiple completed trials in humans and rodents. This area of inquiry has tremendous potential to legitimize exercise during cancer treatment in a way that research on symptoms and side effects does not. In fact, it could be said that if we can establish that exercise improves treatment efficacy, tolerance, or completion, it could shift the field of exercise oncology from a "nice to have" to a "need to have." This may be a higher priority for this reason, as it could also push forward the issues regarding behavior, logistics, and policy of making exercise happen during treatment.

Exercise from the End of Treatment to the End of Life

There are a number of outcomes for which there is sufficient evidence for benefit among cancer survivors who have completed treatment, many of which were reviewed in the paragraphs above. Outcomes for which there is a need for further

investigation include cardiotoxicity and energetics. Further, populations for whom additional exercise oncology research is particularly needed include the advanced cancer, metastatic disease, and those receiving palliative care. It is notable that within Chaps. 12 and 13, which review these outcomes in depth, there is considerable attention paid to the logistical issues of making exercise commonplace in the care of cancer survivors. Given that these issues arise throughout this text, behavior, logistics, and policy issues may be considered central to the expansion and success of practice of exercise oncology in the clinical setting.

Behavioral and Logistical Issues, Multidisciplinarity, and Policy

Challenges relating to the behavioral, logistical, multidisciplinarity, and policy aspects of dissemination and implementation of exercise programming from the point of cancer diagnosis and for the balance of life were intended to be covered just in the last section of the text. But as can be seen by reading the full text, these issues came up in most of the chapters. The evidence base for exercise oncology has expanded and deepened to the extent that many in the field have stopped asking *whether* we should be implementing exercise, and turned their attention to determining *how* to make this happen instead.

Toward that goal, there are clearly behavioral issues to overcome, and Chap. 17 indicates that additional evidence is needed to understand how to alter the behaviors not just of survivors, but of their families, peers, friends, and healthcare providers. Researchers are urged to attend to contextual factors, as well as individual-level characteristics in attempting to promote exercise among survivors. Identification of "active" ingredients, use of "stepped care" approaches, and use of newer approaches to intervention design (e.g., Multiphasic Optimization Strategy, Sequential, Multiple Assignment Randomized trials) are further recommendations for future behavioral research in exercise oncology.

Chapter 18 covered the issues relating to the logistics of making exercise standard practice after a cancer diagnosis. The authors point to three specific issues to be addressed in order for this mission to be accomplished. First, they call for expansion of the evidence-based physical activity programs for survivors. Second, they call for the provision of patient-centered screening and referral of cancer survivors to exercise services/programs. Finally, they call for expansion of dissemination and implementation research to test service delivery models for evidence-based exercise services/programs. The work to accomplish these goals will undoubtedly require examination of models to help the various disciplines involved in exercise oncology to collaborate toward the betterment of patient outcomes. The challenges of multidisciplinarity include questions of which type of training is best for initial and ongoing screening (e.g., physiatrist, physical therapist, or exercise trainer). These issues are further complicated by the reality that the condition of patients will vary over the

course of the cancer experience. Models of care need to be developed and tested that account for the need for a "hand off" between types of exercise oncology professionals.

Finally, Chap. 20 focuses on the policy levers that may need to be pressed in order for exercise to become standard practice throughout the cancer experience. The authors point out that there are few policies in place that support exercise oncology practice, and that the payment policies will need to be written carefully, to ensure that health systems are appropriately incentivized to offer exercise services/programs to cancer patients. There has been little to no policy research completed relevant to exercise oncology. This may be particularly low hanging fruit to make progress in making exercise standard for cancer patients.

Opportunities that Span Beyond One Section

For exercise to become standard of practice in cancer prevention, treatment, or survivorship will likely require coordination of activities across the fields of epidemiology, clinical science, and preclinical science. There are multiple examples where it will not be logistically possible to complete a randomized controlled trial (RCT) to test the efficacy of exercise for some long-term outcome (e.g., incident cancer, precise dose–response curves for multiple cancer health-related outcomes). In such cases, the best we can hope for is triangulation of evidence across multiple fields of study. If there is no RCT, but large well-conducted cohort studies and preclinical studies show consistent evidence of effect, this could be noted as strong indication of a causal effect. Exercise is not the only exposure for which this is true. Research on tobacco and cancer risk similarly triangulates evidence across preclinical, epidemiologic, and clinical research to draw strong conclusions that drive policy, clinical guidelines, and public health recommendations.

Further, there is a need for the various clinical disciplines who "practice" exercise oncology to learn how best to coordinate their efforts for the betterment of patient outcomes. Patients who have worsening of symptoms while participating in a community-based exercise program should be referred back into the medical system, and patients who improve after physical therapy should be referred out of the medical system and into community programming.

Conclusion

In conclusion, while the field of exercise oncology has grown exponentially over the past decade, it is primed for yet another decade of exponential growth. It is the sincere hope of many that by 2030 patients will be offered exercise programming as a matter of course during the cancer experience. It is the belief of many that this goal is achievable.

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