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Exercise Guidelines for Cancer Survivors: Consensus statement from International Multidisciplinary Roundtable

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Abstract

Purpose: The number of cancer survivors worldwide is growing, with over 15.5 million cancer survivors in the United States alone – a figure expected to double in the coming decades. Cancer survivors face unique health challenges as a result of their cancer diagnosis and the impact of treatments on their physical and mental well-being. For example, cancer survivors often experience declines in physical functioning and quality of life, while facing an increased risk of cancer recurrence and all-cause mortality compared to persons without cancer. The 2010 American College of Sports Medicine Roundtable was among the first reports to conclude that cancer survivors could safely engage in enough exercise training to improve physical fitness and restore physical functioning, enhance quality of life, and mitigate cancer-related fatigue.

Methods: A second Roundtable was convened in 2018 to advance exercise recommendations beyond public health guidelines and toward prescriptive programs specific to cancer type, treatments and/or outcomes.

Results: Overall findings retained the conclusions that exercise training and testing was generally safe for cancer survivors and that every survivor should “avoid inactivity”. Enough evidence was available to conclude that specific doses of aerobic, combined aerobic plus resistance training, and/or resistance training could improve common cancer-related health outcomes, including anxiety, depressive symptoms, fatigue, physical functioning, and health-related quality of life. Implications for other outcomes, such as peripheral neuropathy and cognitive functioning, remain uncertain.

Conclusions: The proposed recommendations should serve as a guide for the fitness and health care professional working with cancer survivors. More research is needed to fill remaining gaps in knowledge in order to better serve cancer survivors, as well as fitness and healthcare professionals, to improve clinical practice.

Keywords

cancer survivorship; exercise prescription; safety

1. INTRODUCTION

In the last decade, the United States has seen a 27% decline in cancer deaths due to early detection and improved treatments for cancer. In turn, the number of cancer survivors is growing, with over 15.5 million cancer survivors in the United States - a figure that is expected to double by 2040(1). Improved prognosis has created a growing need to address the unique health issues facing cancer survivors that result from the disease, its treatment, and related comorbid conditions. For example, the symptom of fatigue can persist in 25% of cancer survivors many years after their treatment has ended and contributes to difficulty returning to work, independent living and poor quality of life(2). Furthermore, risk of developing of heart disease may be elevated by some cancer treatments and cardiovascular mortality is emerging as a major competing cause of death in cancer survivors along with cancer recurrence(3, 4). Cancer is also a disease strongly linked with aging, and almost half of survivors are older than 70 years(5). The adverse synergistic effects of age, cancer treatment, and related sequelae increase the total burden of cancer. Historically, clinicians

advised cancer patients to rest and to avoid physical activity, but early exercise research in the 1990's and 2000's challenged this advice.

In 2010 the American College of Sports Medicine convened a Roundtable meeting composed of a team of clinical and research experts in the field of cancer and exercise to develop the first set of exercise guidelines for cancer survivors(6). Drawing on studies mainly in breast and prostate cancer survivors, the key findings from this review were that exercise training was generally safe and well tolerated during and after cancer treatment and could elicit improvements in some health outcomes. There was sufficient evidence to conclude that exercise could improve physical fitness, physical functioning, quality of life, and cancer-related fatigue. However, given the limited number of rigorously designed studies at that time, there was insufficient evidence to inform specific exercise prescriptions for any of these outcomes nor by cancer site or treatment type. Thus, the 2010 Roundtable recommendations largely followed the 2008 Physical Activity Guidelines for adults with chronic conditions to aim for at least 150 minutes per week of aerobic activity, two or more days a week of resistance training, and stretch major muscles groups daily when possible, with specific exercise testing and program modifications based on health status and cancer and treatment-related side effects(7). At a minimum, survivors were urged to “avoid inactivity” and be as physically active as possible(6).

The 2010 ACSM recommendations came with the expectation that they would be updated as the evidence grew and indeed, since that landmark publication the number of randomized controlled exercise trials in cancer survivors has increased by 281% (PubMed Search completed March 2018) to over 2500 published randomized controlled trials. Moreover, an increasing number of calls for the integration of exercise into clinical cancer care have since been issued (8–11). Thus, in 2018 the ACSM International, Multidisciplinary Roundtable on Physical Activity and Cancer Prevention and Control was convened to bring together an international group of exercise and rehabilitation professionals and organizations with the goal to update recommendations based on current evidence. The Roundtable meeting took place on March 12–13, 2018 in San Francisco, California, USA, with 40 representatives from twenty organizations across the world who came together to sponsor and attend this meeting (Table 1). Roundtable members were invited to participate based on their clinical and scientific expertise and were asked to contribute in one or more of the following areas: 1) Role of exercise in cancer prevention and control; 2) Efficacy of exercise to improve cancer-related health outcomes (acute, late and long-term effects); and, 3) Translation of evidence into the clinical and community settings. The outcome of the work in each of these areas would be three separate, but related publications. The manuscripts were circulated to professional organizations for review and to obtain their official endorsement.

This paper will update evidence-based guidelines for exercise testing, prescription and delivery in cancer survivors. As it was acknowledged that the general exercise recommendations put forward in 2010 may be unachievable for cancer survivors with physical limitations and that benefits may come from less exercise, a particular goal of the 2018 Roundtable was to develop more granular exercise prescriptions for distinct cancer-related health outcomes to better guide fitness and other healthcare professionals who train or care for cancer survivors. In the following sections we: 1) describe the evidence review

process and decisions for generating exercise prescriptions for specific cancer-related health outcomes; 2) provide evidence-based FITT (frequency, intensity, time, type) prescriptions for outcomes with sufficient evidence (as outlined below); and 3) provide updates to the 2010 guidelines around exercise testing and training, including special considerations and safety precautions, specific to cancer survivors. We conclude by acknowledging the limitations of this latest Roundtable and suggest directions for future updates.

2. UPDATE TO EVIDENCE-INFORMED EXERCISE PRESCRIPTIONS

2.1 Overview

Two a priori decisions were made by consensus at the Roundtable Meeting. The first was to develop a list of cancer-related health outcomes with a high degree of clinical relevance for which exercise may have therapeutic benefit (BOX 1). The second was to focus the review of evidence primarily on traditional modalities of exercise including aerobic, resistance or combined aerobic plus resistance training on relevant health outcomes. A brief discussion on other modalities of exercise (e.g., yoga) is provided at the end of the paper. Three additional decisions were made by the writing team early on in the writing process where it was agreed upon by consensus that: 1) components of physical fitness (e.g., aerobic capacity, muscular strength/endurance) would not be categorized as cancer-health related outcomes, but would be used to evaluate the adaptability and responsiveness of cancer survivors to specific modes of exercise training; 2) exercise prescriptions would only be generated for outcomes where there was sufficient evidence on the efficacy of exercise to improve a given outcome; 3) beyond each outcome, the exercise prescriptions could not be further specified by tumor type, phase of treatment or type of treatment due to the lack of sufficient evidence to do so in a robust manner. The implications of these limitations are discussed later in the paper.

2.2 Methodology for Evidence Review

To efficiently evaluate and provide a rich synthesis of the evidence, a review of published randomized controlled trials, systematic reviews and meta-analyses for cancer-related health outcomes (Box 1) using Medline/PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, CINAHL, the Physical Therapy Evidence Database (PEDro), and the Cochrane Collaboration. A search was conducted from June-August 2018, for papers published as of June 1, 2018, using standardized search terms for cancer and exercise, in combination with search terms for the list of key cancer-related health outcomes (Supplemental Materials). For each outcome, two writing team members reviewed the resulting systematic reviews and meta-analyses to identify the most recent, relevant, and high quality publications that could facilitate evaluation of the state of science around efficacy of exercise for a particular outcome. If no systematic reviews and meta-analyses were identified, the available RCTs were reviewed.

A decision framework adapted from the Dutch Physical Activity Guidelines(12) was applied to first determine whether or not there was sufficiently strong evidence to conclude that exercise improved specific outcomes and in turn, warrant generation of an evidence-based FITT prescription (Figure 1). Evidence for a given outcome was judged to be strong when there were a substantial number of RCTs (> 5), the aggregate sample size was large

(n>150), and the beneficial effect of exercise was observed consistently across studies. For outcomes with a smaller number of RCTs (<5) or where the overall effect of exercise was inconsistently observed or null, the level of evidence for an exercise benefit was judged as insufficient. For such cases, a FITT prescription was not generated and only a summary of current evidence and research recommendations were provided.

During the review process, authors felt that an intermediate category should be considered for outcomes with >5 RCTs and an aggregate sample >150, yet heterogeneity for evidence of an effect in cancer survivors. In these cases, if there were a consistent number of high quality RCTs (designed and powered on the outcome of interest as the primary endpoint) and that reported findings that were congruent with established evidence on the same outcome in non-cancer populations, the evidence of exercise benefit for these outcomes was judged as moderate and a FITT prescription was generated. However, more research would be needed to confirm the exercise recommendation for these outcomes in cancer survivors.

The next step was to define exercise prescriptions that conformed to the FITT formula and outlined the type and dose of exercise expected to improve a given outcome. To streamline the process, the evidence used to inform each exercise prescription was derived from high quality systematic reviews and meta-analyses which also often provided separate analyses on efficacy by FITT components to identify the most optimal exercise type, time, intensity or frequency to improve a given outcome. However, if the quality of systematic reviews was deemed low (AMSTAR rating <7), individual high-quality RCTs were used to derive the prescription. FITT prescriptions and accompanying summary of the literature, which informed them, were presented to the full writing team during a series of conference calls for discussion and expert consensus (September – October 2018).

2.3 Strong Evidence

For the following cancer-related health outcomes, there was consensus that benefit has been consistently demonstrated and a FITT prescription was developed. Details of each FITT prescription, including any unique considerations, by outcome are provided in Table 2. When interpreting and applying a prescription, the exercise professional should be mindful that the evidence is often disproportionately from trials in a single cancer type (i.e., breast), but the prescription is assumed to generalize across cancer types unless otherwise specified. In addition, studies often did not specifically target enrollment of individuals with the poorest initial values of an outcome (e.g, high fatigue, low bone density) thus the efficacy of a FITT prescription may or may not generalize to cancer survivors in greatest need.

2.3.1 Anxiety—A dose of moderate intensity aerobic training three times per week for 12 weeks or twice weekly combined aerobic plus resistance training for 6–12 weeks can significantly reduce anxiety in cancer survivors during and after treatment(13–17). Based on sufficient evidence, it does not appear that resistance training alone reduces anxiety. There is not sufficient evidence to determine whether or not there is a dose response relationship between exercise intensity and changes in anxiety. Improvements in anxiety appear to be greater in supervised training programs or those having a larger supervised component than those that are predominantly unsupervised or home-based.

2.3.2 Depressive Symptoms.—Moderate intensity aerobic training performed three times per week and for at least 12 weeks or twice weekly combined aerobic plus resistance training lasting 6–12 weeks can significantly reduce depressive symptoms in cancer survivors during and after treatment(18, 19). Based on sufficient evidence, resistance training alone does not seem to be effective for this outcome. Based on results from high quality trials of aerobic training, there may be a dose-response effect where higher volumes of aerobic exercise (90 min vs. up to 180 min/week) leads to better symptom reduction. Improvements in depressive symptoms appear to be greater in supervised training programs or those having a larger supervised component than those that are predominantly unsupervised or home-based.

2.3.3 Fatigue—For training programs that last at least 12 weeks, engaging in moderate intensity aerobic training three times per week can significantly reduce cancer-related fatigue both during and after treatment(20–23). Moderate intensity combined aerobic plus resistance training sessions performed 2–3 times per week or twice weekly moderate intensity resistance training may also be effective(21, 24–26), and the latter particularly in prostate cancer(27). The effect of exercise was strongest for moderate to vigorous intensity exercise whereas the effect for low intensity training was weak and this level of exercise is unlikely to reduce fatigue(22, 24, 26, 28). Whether or not more exercise translates to less cancer-related fatigue remains unclear, though there is suggestive evidence that the reductions in fatigue are greater with exercise sessions longer than 30 minutes and programs longer than 12 weeks compared to less exercise(29). There is insufficient evidence for a linear dose response since going beyond 150 minutes per week of aerobic exercise does not appear to result in the greatest reductions in fatigue. The efficacy of exercise for this outcome appears to be independent of the level of supervision and/or setting for training(21, 27, 30).

2.3.4 Health-related Quality of Life (HRQoL)—Combined moderate intensity aerobic and resistance exercise performed 2–3 times per week for at least 12 weeks results in improvements in HRQoL both during and after treatment(17, 31, 32). The benefit of combined aerobic plus resistance training programs appears more potent than programs consisting of only aerobic or resistance training(32). Though enough evidence favored the efficacy of exercise to improve HRQoL, it should be noted that this particular outcome is a construct that encompasses many factors and may have a more variable response than by individual domains. For example, improvements seems to be more robust if the physical functioning domain of HRQoL is the primary outcome and this will be covered separately. Improvements in HRQoL appear to be greater in supervised training programs or those having a larger supervised component than those that are predominantly unsupervised or home-based.

2.3.5 Lymphedema—There is a history of clinical recommendations to refrain from aerobic or resistance training in order to avoid onset or exacerbation of lymphedema(33, 34). For this particular outcome, an evidence-based exercise prescription is designed for safety or no harm, versus the benefit of exercise to prevent lymphedema or improve lymphedema symptoms, and limited to addressing upper extremity breast cancer-related lymphedema(35–

37). For resistance training, a general progressive program focused on large muscle groups performed 2–3 times per week, with the principle of “start low, progress slow” is safe when supervised by a fitness professional(38–42). Insufficient evidence exists to conclude whether or not starting a resistance training program *without* supervised instruction is safe for women with or at risk for lymphedema after breast cancer. To date, there is insufficient evidence to draw conclusions for aerobic exercise. In general, aerobic exercise seems to be safe, with no significant increase in number of lymphedema-related adverse events reported in studies investigating aerobic exercise(17). Based on preliminary evidence(43), the effects seen in breast cancer may not translate for lymphedema following head and neck, bladder, melanoma, gynecologic, or other cancer sites.

2.3.6 Physical Function—Moderate intensity aerobic training, resistance training or combined aerobic plus resistance training performed three times weekly for 8–12 weeks can significantly improve self-reported physical function(31, 32, 44). Broadly, supervised exercise appears to be more effective than unsupervised or home-based interventions(32), although unsupervised programs may be effective in older cancer survivors(44). Further, there is some evidence to suggest that if the intervention is unsupervised, physical function could improve with higher weekly energy expenditure (MET-hr/week) but not weekly exercise duration (min/week)(32). It should be noted that these results are based on self-reported physical function, not objective measures where the evidence base on these outcomes remains immature and more challenging to aggregate due to the variation and limitations of assessment techniques.

2.4 Moderate Evidence

2.4.1 Bone Health—Two recent systematic reviews in cancer survivors concluded that across all trials the evidence for exercise to improve bone health is inconsistent(45, 46), though RCTs that were designed with bone health as the primary outcome were largely consistent with the exercise recommendations in the ACSM Position Stand for exercise and bone health(47). In cancer, the majority of evidence is derived from trials in breast and prostate cancer patients in the post-adjuvant treatment setting, which indicates that a one-year supervised program of combined moderate-vigorous intensity resistance *plus* high impact training (i.e., exercise that generates ground reaction forces above 3–4 times body weight) performed 2–3 days per week is the most consistently efficacious modality of exercise to improve bone health (e.g., slow loss or slightly improve bone mineral density at the lumbar spine and hip). In contrast, aerobic training, particularly walking, does not appear to provide a sufficient stimulus to improve bone outcomes, results that are consistent with RCTs in persons without cancer. There is insufficient evidence to determine if resistance training alone improves bone outcomes.

In non-cancer populations, whether or not resistance plus impact training programs are safe for individuals with osteoporosis remains controversial(48), thus at this time this exercise prescription may not be safe for cancer survivors with bone fragility associated with osteoporosis or bony metastases in the hip or spine (see section 5). Furthermore, it may not be appropriate 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 that this recommendation is effective and safe for cancer survivors.

2.4.2 Sleep—Two recent systematic reviews in cancer survivors(49, 50) provided mixed evidence for overall sleep quality, indicating either a positive effect of walking(49), or no effect of exercise(50). Four recent RCTs not included in either systematic review have shown consistent evidence of small to moderate effect sizes on overall sleep quality for aerobic training(51), in addition to walking specifically(52, 53) and one study reported evidence of benefit for resistance training(31). In non-cancer populations, there is strong evidence that moderate to vigorous intensity aerobic training is associated with better overall sleep quality in the general population(54) and there was some evidence showing benefit for specific characteristics of sleep, such as total sleep time, sleep onset latency, and sleep efficiency. Overall, moderate intensity aerobic training, particularly walking, 3–4 times per week, for 30–40 minutes per session over 12 weeks is recommended.

2.5 Insufficient Evidence

Insufficient evidence for a specific outcome does not mean that cancer survivors facing these cancer-related health outcomes will not benefit in other ways from engaging in physical activity or should remain sedentary. Rather there is insufficient evidence showing that exercise is beneficial for these specific outcomes based on current evidence and this creates an obvious gap in knowledge the research community must fill.

2.5.1 Cardiotoxicity—The effect of exercise to prevent or ameliorate cardiotoxicity is an emerging field of research and promising results for a protective effect of exercise in animal models and some novel evidence in humans for cardiac function(55), including measures of left ventricular function(55), and vascular endothelial function, measured as flow-mediated dilation(56). More research is needed to understand the impact of various types of cancer, cancer treatments and exercise prescriptions on both cardiac and vascular function.

2.5.2 Chemotherapy induced peripheral neuropathy—To date, there are too few high quality trials to interpret the potential of the benefits of exercise for preventing and/or managing chemotherapy-induced peripheral neuropathy and related side effects, such as balance impairment and falls(57). In general, exercise appeared safe in the few published studies, however, the degree of improvement varied for this outcome, and other related outcomes, such as mobility and balance. Future research should include well controlled exercise interventions with chemotherapy-induced peripheral neuropathy as a primary outcome, using both patient-reported outcomes and objective assessment of neuropathy, balance and mobility, and also rigorously evaluate the safety of training in this group due to the known risk of falls.

2.5.3 Cognitive function—While promising results from animal studies are emerging for a protective effect of aerobic training on cancer treatment related changes in cognitive function, to date, the evidence in humans is limited(58). The majority of human studies, so far, have been conducted in breast cancer survivors, using self-reported measures of cognitive function, and report inconsistent results. While there is compelling evidence

of a positive effect of exercise on cognitive function in older adults and other clinical populations(59), specific to cancer, more research is needed in cancer survivors where cognitive function is the primary outcome, and this outcome is assessed by both self-reported and standardized objective measures of cognitive function.

2.5.4 Falls—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(60, 61).

2.5.5 Nausea—While a commonly reported benefit of exercise during chemotherapy, there is limited data from high quality trials with nausea as a primary endpoint to support this finding outside of an early study demonstrating a reduction by Winningham et al.(62). Future research could examine the effect of well controlled exercise interventions on nausea in highly emetogenic regimens to determine if there is an effect. These studies should account for antiemetic use, duration and intensity of nausea, and function.

2.5.6 Pain—To date most published controlled trials in cancer survivors have examined non-specific pain, and included pain as a secondary outcome, which limits the interpretation of the research. There is early evidence from two high-quality controlled trials where pain was the primary outcome that a combined home-based aerobic plus supervised resistance training intervention in women with breast cancer significantly reduced arthralgia associated with aromatase inhibitor therapy(63) and a supervised resistance training intervention focused on the upper extremity significantly reduced in shoulder pain in individuals with head and neck cancer(64). However, more research is needed specifically focused on cancer-related pain. 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.

2.5.7 Sexual Function—The majority of research to date has been in men with prostate cancer(65, 66) and there is insufficient evidence from controlled trials investigating the effect of exercise on sexual function during or after cancer therapy. Early promising results for a positive effect of exercise on sexual function among prostate cancer patients treated with androgen deprivation therapy has been reported in some trials(67, 68) but not others(69). While there is compelling evidence of a positive effect of exercise on sexual function in the general population, for both women(70) and men(71), the significant effects of cancer therapies on hormonal and anatomical/functional changes (i.e., nerve sparing

versus non-nerve sparing surgeries in prostate cancer) preclude the ability to extrapolate those findings to the cancer population.

2.5.8 Treatment Tolerance—Treatment tolerance (i.e., completion of or adherence to planned therapy) is a complex outcome that likely varies by cancer type, treatment modality (i.e., radiation therapy, chemotherapy, hormone therapy, immunotherapy), and even specific drug(s) and protocols. Consequently, determining the effects of exercise on “treatment tolerance” is a challenging goal and may make it difficult to achieve a high degree of generalizability. A recent systematic review of exercise and chemotherapy completion rate concluded that, while promising, the evidence for an exercise benefit to chemotherapy tolerance is insufficient(72). The effects of exercise on treatment tolerance for radiation therapy, hormonal therapy (i.e., aromatase inhibitors or androgen deprivation therapy), targeted therapies or immunotherapy is currently unknown. To understand the effect of exercise on treatment tolerance, studies would need to be conducted for each combination of cancer type and treatment regimen.

2.6 Limitations

The FITT prescriptions provided for several outcomes aim to serve as guidelines for fitness and healthcare professionals working with cancer survivors. However, the development of these guidelines had some key limitations that should be kept in mind when working with individual clients. The majority of available literature is still in the most common cancers, namely early stage breast cancer and prostate cancers, which limits the ability to extrapolate to other cancer types or advanced cancers. Though, it could be reasonably assumed that in the absence of any unique safety concerns for survivors of other types of cancer that the efficacy of exercise on various outcomes would be similar for survivors with early stage cancers other than breast and prostate cancer. However, differences among cancer survivors by cancer type are known to exist (i.e., demographics, prognosis, treatments received and associated side effects) and further, there is very little information regarding the feasibility, safety or benefits of exercise in individuals living with advanced cancer. More research is needed to advance the level of specificity available in the exercise oncology literature to serve a broader range of cancer types and stages(73). In addition, there has historically been incomplete reporting of compliance to a prescribed FITT program in published studies, likely because tracking and quantifying compliance can be burdensome (74–76). Thus, it remains possible that some proportion of cancer survivors may not be able to tolerate the evidence-based FITT, as explicit reporting of adjustments to the exercise prescription (i.e., dose modification) based on tolerance of individuals has been limited. Thus, the fitness or healthcare 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. Furthermore, understanding the specific efficacy of exercise for a particular outcome is hampered by the fact that the majority of research to date does not consider the training principle of initial values by limiting enrollment to individuals experiencing the specific outcome of interest (i.e., those with sleep issues or high level of fatigue), rarely examines potential moderators of the exercise response (i.e., baseline functional capacity), and often draws conclusions about outcomes that are secondary to the intended design of the study. Finally, a further understanding of dose response is limited

by a paucity of trials that directly compare two or more levels of exercise training (e.g., high versus low intensity exercise) on cancer-related outcomes(77) or compare settings (e.g., supervised versus home-based)⁷⁵. Clearly, more research to address these knowledge gaps is warranted so that recommendations can continue to improve in scope and specificity.

2.7 Other exercise modes

There is also increasing interest in the safety and efficacy of types of exercise that fall outside of traditional modes of aerobic and resistance training. In a recent systematic review of the role of yoga in symptoms management for cancer survivors, yoga both during and after cancer treatment was reported to improve quality of life and fatigue, while further research is needed to confirm the observed potential to improve sleep, depressive symptoms, anxiety/distress, and cancer-related cognitive change(78). However, the literature is reflective of practices for many different types of yoga, including those that incorporate non-exercise features such as breathing or meditation and which use a wide variety of prescriptions (e.g., frequency, duration, with/without home practice), making it difficult to generate a definitive prescription. While there is also insufficient evidence at this time for a definitive prescription around safety and efficacy for other types of exercise for cancer survivors, such as dragon boating(79, 80), recreational sports(81), wall/rock climbing(82), triathlon(83), or high intensity interval training(84), research is on-going.

3 EFFECTS OF CANCER TREATMENT AND ADVERSE EFFECTS RELEVANT TO EXERCISE

To best evaluate a cancer survivor's exercise tolerance and prescribe a safe and effective exercise program, it is necessary for fitness professionals to know about the type and extent (i.e. stage) of cancer a person has. Fitness professionals must also be familiar with the common treatment approaches to cancer, the side effects and symptoms these treatments can cause, and the subsequent impact on exercise tolerance (Table 3). The treatment approach used will differ by type of cancer, stage of disease, cancer subtype, patient health and many other considerations. Treatment modalities may include a combination of surgery, radiation, and systemic therapies, including cytotoxic chemotherapy, newer targeted agents including immune checkpoint inhibitors, and hormonal therapy. When individuals are on active cancer treatment, 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.

The impact of cancer treatment on exercise tolerance may further depend upon the pre-diagnosis health and functional capacity of the individual. Furthermore, 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.

4 MEDICAL CLEARANCE & EXERCISE TESTING

Both the diagnosis of cancer and curative cancer treatments may affect the underlying safety of exercise training. Guidance for the indications of medical clearance prior to exercise testing and/or training, as well as how exercise testing should be adapted for cancer survivors, can be useful for creating a safe and effective exercise prescription. Where this information is available elsewhere and to avoid redundancy, the reader will be referred to specific publications.

4.1 Medical Clearance Prior to Exercise

Given the diversity of tumor types and side effect of different cancer treatments, including the potential acceleration of cardiovascular disease (CVD), the question of 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 is always relevant. Recently, the ACSM updated its pre-participation exercise guidelines for all persons in an attempt to reduce barriers to exercise by removing a requirement for medical clearance for individuals whose risk of an adverse cardiac event during exercise are low, including exercise naïve persons(85). 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. The ACSM pre-participation guidelines do not explicitly address risks for adverse events and/or injury during exercise that are specific to the adverse effects of cancer treatment. Therefore, we have referred to the National Comprehensive Cancer Network (NCCN) Survivorship Guidelines(8) 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 4).

4.2 Exercise testing

Ideally, cancer survivors should receive a comprehensive assessment of all components of health-related physical fitness (i.e., cardiorespiratory fitness, muscle strength and endurance, body composition and flexibility), with some specific cancer-specific considerations (BOX 2), 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 required to start low intensity aerobic training (i.e., walking or cycling), resistance training with gradual progression, or a flexibility program in most survivors. Medical clearance may still be indicated as previously described depending on exercise and health history and presence of cardiovascular, renal or metabolic symptoms(85).

5 EXERCISE SAFETY & TRAINING TOLERANCE

5.1 Safety of exercise training

The overall conclusion from the 2010 Roundtable was that exercise is generally safe for cancer survivors(6) and this has not changed based on the majority of studies conducted since that time. It should be recognized 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 breast cancer survivors(17, 31, 32). Hence the individuals enrolled in studies commonly meet pre-specified eligibility criteria for age, comorbidities, physical ability, largely based out of academic and/or medical centers, and were willing to participate in research. This often results in a sample that is healthier or with higher physical function and exercise motivation that may not fully generalize to the broader population of cancer survivors. Depending on the nature and extent of a survivor's presenting problems they may not be able to adequately and/or safely engage in the levels of exercise outlined in this recommendation. In these cases, we again refer to the NCCN guidelines (Table 4). Physical therapy or medical evaluation might be a bridge to inform appropriate modifications to an individual's exercise program and/or correct toxicities, impairments and limitations that prevent a survivor from working toward recommended levels of exercise.

5.2 Exercise Tolerance

Exercise has well established health benefits in persons without cancer, thus a key consideration in exercise trials has been whether or not cancer survivors can tolerate the doses of exercise known or hypothesized to effectively improve physical fitness and in turn, associated cancer-related outcomes. Research to date supports the potential of cancer survivors to respond positively to an exercise training stimulus by improving individual components of physical fitness, including cardiorespiratory fitness (i.e., VO₂peak)(86), muscular strength and endurance(87, 88), body composition(89). However, an individual's 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), or demographics factors (i.e., age)(90). Furthermore, during active treatment an individual's ability to tolerate exercise may fluctuate from day to day or week to week. Understanding of these interactions is a topic of ongoing research, especially with the emergence of novel therapies.

Specific to cardiorespiratory fitness, during chemotherapy treatment there is a well-documented decline in cardiorespiratory fitness, as measured by VO₂peak or 6-minute walk test(4). Randomized trials of aerobic exercise during adjuvant chemotherapy demonstrate a preservation of, or an improvement in, cardiorespiratory fitness, especially in those with low initial values(86), while others report better improvement in those with higher initial values(91). Aerobic exercise during adjuvant chemotherapy does not appear to stimulate greater production of red blood cells(92), so improvements in cardiorespiratory fitness are contingent on other central (i.e., cardiac function, plasma volume) and peripheral adaptations (i.e., improved vascularization and mitochondrial enzyme function)(93).

Specific to muscular strength, loss of muscle strength and endurance is common due to deconditioning or as a side effect of cancer treatment. For example, 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(94, 95). In the absence of the anabolic drive from testosterone, men on ADT may not be able to build lean mass in response to resistance training; however, several

based programs, though it is unclear whether or not this is because a higher dose of exercise may be better achieved with supervised training or from other attributes of this setting (i.e., more attention, motivation, reinforcement, selection bias). While a variety of professionals delivered supervised interventions in the research literature (e.g., exercise physiologists, certified exercise instructors, nurses, physical therapists) determining the type of professional that could maximize outcomes was beyond the scope of this paper and the available evidence.

However, the fitness professional should be prepared to create an exercise program that meets their clients' needs. 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(54). There is consistent observational evidence that engaging in physical activity following a cancer diagnosis reduces the risk of cancer-specific and all-cause mortality for individuals diagnosed with early stage breast, colorectal and prostate cancer(104). Special considerations and modifications to exercise programs have been adapted from the NCCN guidelines (Table 5). Finally, as part of the ACSM Roundtable efforts, oncologists are being asked to "Assess, Advise, and Refer", in order to connect cancer survivors to the most appropriate available exercise programming. A registry of programming is available at www.exerciseismedicine.org/movethruca (105).

7 SUMMARY AND FUTURE DIRECTIONS

The 2018 ACSM Roundtable recommendations were made possible due to the increase in the availability of high quality randomized controlled trials of exercise in cancer survivors published after the 2010 recommendations were issued. This allowed for the development of more specific evidence-based exercise prescription to improve common side effects of a cancer diagnosis and treatment, namely anxiety, depressive symptoms, fatigue, health-related quality of life, and physical function, along with safety of exercise training in persons with or at risk of breast-cancer related lymphedema. Future research is needed to determine the efficacy of exercise to improve other outcomes, including those identified here under the emerging or insufficient evidence categories. In addition, the literature remains insufficient for further detailing prescriptions according to cancer type, timing of treatment, and/or types of treatment, while exercise prescriptions were rarely based on studies that directly compared varying FITT components, such as a head-to-head trial of low versus high intensity training. Thus, as the evidence base continues to grow in other cancer sites and keeps pace with the evolution of cancer treatment, as well as trial designs broaden to include multiple treatment arms, the next generation of exercise prescriptions could have the specificity to move exercise oncology toward the same goal as precision oncology where treatment is matched to the specific characteristics of a person's cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1.**List of common acute, long term and late effects of cancer for review of evidence for therapeutic efficacy of exercise and subsequent exercise prescriptions**

• Anxiety
• Bone health
• Cardiotoxicity
• Chemotherapy-induced peripheral neuropathy
• Cognitive function
• Depressive symptoms
• Falls
• Fatigue
• Health-related quality of life
• Lymphedema
• Nausea
• Pain
• Physical function
• Sexual function
• Sleep
• Treatment tolerance

BOX 2.**Exercise testing recommendations:**

- | |
|---|
| <ul style="list-style-type: none"> • 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: |
| <ul style="list-style-type: none"> • 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(85). |
| <ul style="list-style-type: none"> • 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 |
| <ul style="list-style-type: none"> • 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(106) |
| <ul style="list-style-type: none"> • In principle, there is no evidence that the level of medical supervision required for symptom-limited or maximal cardiopulmonary exercise testing need to be different for patients with cancer than for other populations(85). |
| <ul style="list-style-type: none"> • The evidence-based literature indicates 1-RM testing is safe among survivors of breast and prostate cancer without bony metastases(6) |
| <ul style="list-style-type: none"> • 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(107). 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 scope of practice or protocols at a specific site/facility. |
| <ul style="list-style-type: none"> • Older survivors and/or survivors treated with neurotoxic chemotherapy (typical for breast, colon, lung, ovarian cancers) may especially benefit from a standard assessment of balance and mobility to assess fall risk(108) |
| <ul style="list-style-type: none"> • CVD has become a competing cause of morbidity and mortality for survivors of cancer with a favorable prognosis(109). Given the potential for underlying CVD, cancer survivors should be screened for evident or underlying CVD using the ACSM pre-participation guidelines (see below) and if implicated have a cardiopulmonary exercise test prior to beginning an exercise program(110). |

Box 3:**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

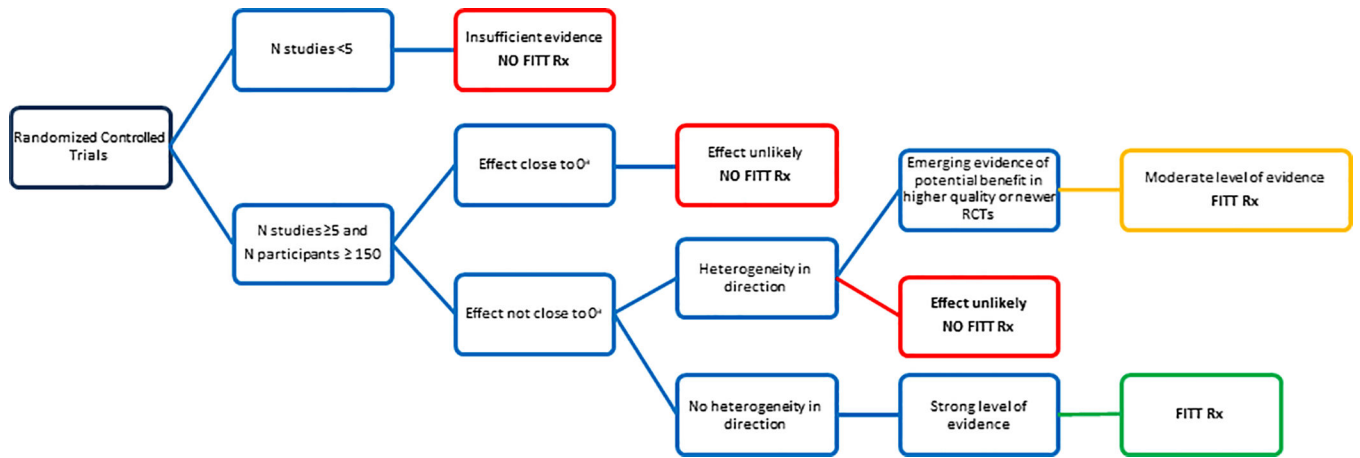


FIGURE 1: Decision tree on the level of evidence for effects (RCT) sufficient to merit an exercise prescription (FITT Rx). aAdapted with permission from Weggemans RM, Backx FJG, Borghouts L, et al. The 2017 Dutch Physical Activity Guidelines. *Int J Behav Nutr Phys Act.* 2018;15(1):58.

Table 1.

Participating organizations

American College of Sports Medicine (ACSM) [*] , [†]	Exercise and Sports Science Australia [*] , [†]
American Cancer Society (ACS) [*] , [†]	German Union for Health Exercise and Exercise Therapy (DVGS) [*] , [†]
American Academy of Physical Medicine and Rehabilitation (AAPMR) [*] , [†]	MacMillan [*] , [†]
American Physical Therapy Association (APTA) [*]	National Cancer Institute (U.S.)
American Congress of Rehabilitation Medicine	National Comprehensive Cancer Network [†]
American College of Lifestyle Medicine [†]	Royal Dutch Society for Physical Therapy (KVDP) [*] , [†]
Canadian Society for Exercise Physiology [*] , [†]	Society for Behavioral Medicine [†]
Centers for Disease Control [†]	Sunflower Wellness [*] , [†]
Commission on Accreditation of Rehabilitation Facilities [†]	

Legend

^{*} Roundtable Partner Organizations

[†] Organizations that provided official endorsement

Table 2. Cancer-related health outcome with sufficient evidence for development of FITT prescription

Outcome	Type†	Intensity	Duration (min) or Sets (reps)	Frequency (sessions per week)	Length (weeks)	Setting (supervised, home-based or combination)	Dose response	Special considerations	Evidence primarily from these cancer types.
Anxiety	Aerobic	60–80% HR _{max} 60–80% VO _{2max} RPE 13–15	30–60	3	12	Supervised more effective	Moderate to vigorous may be more effective than light to moderate	Not known	Breast (majority), prostate, colorectal, gynecological (ovarian, endometrial, cervical), head and neck, lung, hematological cancer
	Resistance	Efficacy not demonstrated	NA	NA	NA	NA	NA	NA	
	Aerobic + Resistance	60–80% HR _{max} 60–80% VO _{2max} RPE 13–15	20–40	2–3	6–12	Supervised or combination of supervised & home-based	None observed	Not known	
Depressive Symptoms		65–85% IRM	2 sets 8–12 reps	2–3	6–12				Breast (majority), prostate, colorectal, hematological
	Aerobic	60–80% HR _{max} 60–80% VO _{2max} RPE 13–15	30–60	3	12	Supervised more effective	Benefit up to 180 min/wk	Not known	
	Resistance	Efficacy not demonstrated	NA	NA	NA	NA	NA	NA	
Fatigue	Aerobic + Resistance	60–80% HR _{max} 60–80% VO _{2max} RPE 13–15	20–40	3	12	Supervised or combination of supervised & home-based	None observed	Not known	Breast (majority), prostate, mixed
		65–85% IRM	2 sets 8–12 reps	2–3	6–12				
	Aerobic	65% HR _{max} 45% VO _{2max} RPE 12	30	3	12	Supervised and unsupervised appear similarly effective	No dose response by intensity; possible > benefits with duration & length of program	No evidence of benefits from light intensity	
	Resistance	60% IRM RPE 12	2 sets 12–15 reps	2	12	Supervised and unsupervised appear similarly effective	None observed	Not known	
	Aerobic + Resistance	65% HR _{max} 45% VO _{2max} RPE 12	30	3	12	Supervised and unsupervised appear similarly effective	None observed	Not known	

Outcome	Type [†]	Intensity	Duration (min) or Sets (reps)	Frequency (sessions per week)	Length (weeks)	Setting (supervised, home-based or combination)	Dose response	Special considerations	Evidence primarily from these cancer types.
Health-related Quality of Life		60% 1RM RPE 12	2 sets 12–15 reps	2	12				
	Aerobic	60–80% HRmax RPE 11–13	30	2–3	12	Supervised more effective	None observed	NA	Breast (majority), prostate, colorectal, lung, head and neck, bladder, gynecological, mixed, hematological cancer, hematopoietic stem cell transplant
	Resistance	60–75% 1RM RPE 13–15	2–3 sets 8–15 reps	2–3	12	Supervised or combination of supervised & home-based	None observed	NA	
	Aerobic + Resistance	60–80% HRmax RPE 11–13	20–30	2–3	12	Supervised more effective	None observed	AT & RT combined most effective	
		60–80% 1RM RPE 12–14	2 sets 8–15 reps	2–3	12				
Lymphedema*	Aerobic	NA	NA	NA	NA	NA	NA	Generally safe, as no significant increase in number of lymphedema-related adverse events reported in RCT of aerobic exercise	Breast cancer-related lymphedema only
	Resistance	60–70% 1RM RPE 15	1–3 sets 8–15 reps	2–3	52	All of the interventions reviewed started with supervision to teach the exercises.	NA	Start resistance a low weight and progress slowly	
	Aerobic + Resistance	NA	NA	NA	NA	NA	NA	NA	
Physical Function	Aerobic	60–85% HRmax 60–85% VO ₂ max RPE 12–13	30–60	3	8–12	Supervised more effective	If unsupervised, requires higher weekly exercise expenditure (unclear what the threshold is)	NA	Breast (majority), prostate, colorectal, lung, bladder, head and neck, hematological cancer, hematopoietic stem cell transplant
	Resistance	60–75% 1RM RPE 13–15	2 sets 8–12 reps	2–3	8–12	Limited evidence to determine benefit of unsupervised	NA	NA	
	Aerobic + Resistance	60–85% HRmax 60–85% VO ₂ max RPE 12–13	20–40	3	8–12	Both supervised & home-base suitable in older adults	NA	Community-based interventions that met in groups & used behaviour change strategies may produce larger	
		60–75% 1RM RPE 13–15	2 sets 8–12 reps	2–3	8–12				

Outcome	Type [‡]	Intensity	Duration (min) or Sets (reps)	Frequency (sessions per week)	Length (weeks)	Setting (supervised, home-based or combination)	Dose response	Special considerations	Evidence primarily from these cancer types.
								effects in older adults	

[‡]Mode: For aerobic activity, this includes walking, cycling ergometer and other forms of traditional aerobic exercise; for resistance, this includes machine-based and free weights.

Legend

* recommendation for breast cancer-related lymphedema only.

Abbreviations: NA, not applicable.

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Legend

- ^a Depends on type or target of agent
- ^b Especially common with PI3kinase inhibitors
- ^c Can occur in any type of cancer when and where lymph nodes are surgically resected and/or radiation over lymph nodes.

Abbreviations: CVD, cardiovascular disease; GI, Gastrointestinal.

Table 4.

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 [†]
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 [†]

Legend

[†] 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)).

* Medical evaluation – per NCCN guidelines for specific symptoms and side effects

Table 5.

Exercise programming considerations for specific cancer survivors

Consideration	Recommendations.
Bone loss / bone metastases:	<ul style="list-style-type: none"> • Avoid contraindicated movements 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 • Specific guidance on how to modify exercise programs based on the site of bony lesions is provided elsewhere(107, 111) • Preventing falls must also be a goal of therapy, since falls play an important role in fracture etiology (112). • Be aware of signs and symptoms of bone metastases in survivors, as well as common locations where these occur (i.e., spinal vertebrae, ribs, humerus, femur, pelvis). Bone pain can be an initial sign of skeletal metastases thus, exercise trainers should refer survivors who report pain back to the medical team for clinical evaluation prior to continuing exercise
Lymphedema	<ul style="list-style-type: none"> • To date, there is insufficient evidence to support or refute this clinical advice to wear a compression garment during exercise to prevent or reduce symptoms of breast cancer-related upper body lymphedema. Therefore, it is recommended that exercise professionals provide this information as part of client education and defer to an individual client's preference regarding use of a compression sleeve. • Being overweight or deconditioned have been associated with a higher risk of developing cancer-related lymphedema in observational studies, at this time there is insufficient evidence that weight loss or improving aerobic fitness can lower the risk of developing cancer-related lymphedema(113).
Older adults	<ul style="list-style-type: none"> • 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(114–116) • Exercise professionals will need to combine ACSM guidelines on exercise programming for older adults(117) 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	<ul style="list-style-type: none"> • 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 is required. Avoid use of a Valsalva maneuver(118, 119). • 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.
Peripheral Neuropathy	<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> ○ 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(120)
Stem cell transplantation	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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(121). • 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.
Sun Safety	<ul style="list-style-type: none"> • In addition to melanoma survivors(122), survivors of cancer at other primary sites may be at increased risk for secondary skin cancers(123) • Exercise professionals should recommend that cancer survivors engage in sun protective practices when exercising outdoors(124).