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Putting Exercise into Oncology Practice: State-of-the-Science, Innovation, and Future Directions

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Abstract

Physical activity provides numerous health benefits for cancer survivors. This review provides a summary of the evidence supporting the efficacy of physical activity to improve patient-reported and physiological outcomes during and after cancer therapy, discusses observational studies that have reported associations of physical activity with cancer outcomes and prognosis, summarizes ongoing phase III randomized trials of physical activity with clinical disease endpoints in cancer survivors, describes randomized trials of physical activity that have examined biomarkers hypothesized to relate to cancer outcomes and prognosis, reviews current guidelines for physical activity promotion among cancer survivors, and provides recommendations for novel strategies to disseminate and implement this evidence into clinical oncology practice to optimize patient outcomes.

Keywords

physical activity; cancer survivorship; guidelines; lifestyle; oncology

Introduction

A rapidly increasing volume of evidence suggests that physical activity may provide numerous health benefits for cancer survivors. Observational cohort studies demonstrate that individuals who report higher levels of physical activity after a diagnosis of cancer have a lower risk of disease recurrence and cancer related mortality as compared to inactive individuals with cancer. Translational studies have been launched to elucidate the biologic or biobehavioral mechanisms through which physical activity may prevent disease recurrence and cancer specific mortality. Randomized clinical trials have consistently demonstrated that physical activity interventions both mitigate common symptoms that impair quality of life and improve physiological outcomes in cancer survivors. This accumulating volume of

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evidence has led organizations such as the American College of Sports Medicine, American Cancer Society, National Comprehensive Cancer Network, and other international exercise and oncology groups to produce evidence-based guidelines for physical activity promotion in cancer survivors.

This review discusses observational studies that have reported associations of physical activity with cancer outcomes and prognosis, summarizes ongoing phase III randomized trials of physical activity with clinical disease endpoints in cancer survivors, describes randomized trials of physical activity that have examined biomarkers hypothesized to relate to cancer outcomes and prognosis, provides a summary of the evidence supporting the efficacy of physical activity to improve patient-reported and physiological outcomes during and after cancer therapy, reviews current guidelines for physical activity promotion among cancer survivors, and offers recommendations for novel strategies to disseminate and implement this evidence into clinical oncology practice to optimize patient outcomes.

Association between Physical Activity and Cancer Mortality

It is estimated one-in-ten cancer deaths can be attributable to a lack of physical activity.[1] All of the evidence that has examined the association between physical activity and clinical outcomes in cancer survivors, such as disease recurrence or mortality, has been derived from observational studies and necessitate a conservative interpretation since causality cannot be verified. A recent meta-analysis of 38,560 cancer survivors who most commonly had early-stage cancers of the breast, colon and rectum, and prostate demonstrated that higher volumes of self-reported physical activity after cancer diagnosis was associated with a 37% lower relative risk of dying from cancer (Hazard Ratio: 0.63; 95% CI: 0.54–0.73), and this effect size estimate was similar in magnitude across all three common cancer sites.[2] In breast cancer survivors, the relationship between physical activity and cancer-specific mortality was independent of body mass index, menopausal status, and tumor estrogen receptor status.[2] In colorectal cancer, a dose-response relationship between physical activity and cancer outcomes has been seen, such that higher volumes of physical activity (minutes per week) are associated with larger relative risk reductions.[3] In prostate cancer, more vigorous intensities of physical activity are associated with larger relative risk reductions, compared to light- and moderate-intensity physical activity.[4] Additionally, emerging data suggests that sedentary behaviors, such as screen-based activities like TV viewing, and smartphone and computer use, are associated with an increased risk of cancer specific mortality, underscoring the importance of avoiding inactivity.[5]

Randomized Trials Evaluating the Impact of Physical Activity Interventions on Cancer Recurrence and Mortality

There are currently no data from randomized trials evaluating the impact of a physical activity intervention on the risk of cancer recurrence or mortality among individuals diagnosed with cancer. To strengthen the above-described observational literature, there are several ongoing randomized clinical trials that are examining lifestyle-based programs that include a physical activity component on a clinical disease endpoint in patients with early and advanced cancers. The Lifestyle Intervention for Ovarian Cancer Enhanced Survival

(LIVES) randomized trial will examine the impact of a physical activity and dietary modification program (emphasizing fat reduction and increased fruit and vegetable consumption) on progression-free survival among 1,070 individuals diagnosed with advanced ovarian cancer.[6] The Colon Health and Life-Long Exercise Change (CHALLENGE) randomized trial will examine the impact of a three-year physical activity program on disease-free survival in 962 individuals with high-risk stage II or stage III colon cancer.[7] The Intense Exercise for Survival among Men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL-GAP4) randomized trial will examine the impact of a vigorous-intensity aerobic and muscle strengthening exercise on overall survival in 866 individuals with metastatic prostate cancer.[8] The Breast Cancer Weight Loss (BWEL) randomized trial will examine the impact of a two-year weight loss program, including caloric restriction and increased physical activity, on invasive disease-free survival in 3,136 overweight and obese women diagnosed with stage II-III breast cancer.[9] Together, these clinical trials will provide important information regarding the role for physical activity in the prevention of disease recurrence, progression, and mortality in patients with established cancer. The successful completion of these trials will provide the high quality evidence that is necessary to justify the provision and reimbursement of physical activity programs to cancer survivors as a standard of care.[10]

Physical Activity and Biological Outcomes

The specific biologic or biobehavioral mechanisms that link physical activity with cancer prognosis have not been fully elucidated. It is hypothesized that factors such as inflammation, insulin and insulin-like growth factors, sex steroids, and immune function promote a host tumor microenvironment that encourages malignant cell growth and progression.[11] A systematic review examined randomized controlled trials with biomarker endpoints and concluded that physical activity may favorably change circulating concentrations of inflammatory biomarkers, insulin and insulin-like growth factors, sex steroids, and select measures of immune function.[12]

For example, elevated concentrations of insulin (hyperinsulinemia) at cancer diagnosis has been independently associated with poorer prognosis in a number of cancers, including breast and colon.[13,14] Studies in breast and colon cancer survivors demonstrate that physical activity reduces insulin concentrations,[15,16] and changes in insulin concentrations are associated with reductions in circulating tumor cells.[17] Such observations lend support to the hypotheses that these biomarkers mediate the relationship between physical activity and cancer outcomes (e.g., recurrence and survival). Elucidating the biological and biobehavioral mechanisms that mediate the relationship between physical activity and cancer outcomes will provide novel insight into cancer biology by helping to identify new avenues for therapeutic intervention. It is noteworthy that the large clinical trials described in the preceding section that are studying disease endpoints all include robust correlative science sub studies that will rapidly advance this area and offer the opportunity to empirically validate surrogate biomarker measures of cancer prognosis.[6–9]

Physical Activity and Patient-Reported Outcomes in Cancer Survivors

Randomized clinical trials demonstrate that physical activity interventions mitigate common symptoms that impair quality of life in cancer survivors. A systematic review and meta-analysis of 56 randomized controlled trials including 4,068 participants (28 studies with stage I-III breast cancer) demonstrated that physical activity such as aerobic walking or cycling, during and after cancer treatment, significantly reduced cancer-related fatigue (Standardized Mean Difference (SMD) Effect Size: −0.27; 95% CI: −0.37 to −0.17) compared to usual care.[18] Another systemic review and meta-analysis of 40 randomized controlled trials including 3,946 participants (22 studies with stage I-III breast cancer) demonstrated that physical activity after completing cancer treatment significantly improved overall health related quality of life (SMD: 0.48; 95% CI: 0.16 to 0.81), emotional well-being (SMD: 0.33; 95% CI: 0.05 to 0.61), and social functioning (SMD: 0.45; 95% CI: 0.02 to 0.87) and reduced symptoms of anxiety (SMD: −0.26; 95% CI: −0.44 to −0.07) compared to usual care control.[19] An individual patient data meta-analysis of 34 studies including 4,519 participants (70% of study participants with stage I-III breast cancer) highlighted that supervised physical activity programs increase health related quality of life (SMD: 0.13; 95% CI: 0.04 to 0.23) and physical functioning (SMD: 0.22; 95% CI: 0.16 to 0.27) to a larger magnitude compared with unsupervised physical activity programs.[20] Underscoring the importance of promotion of physical activity in oncology, cancer survivors with poor quality of life, high fatigue, and poor physical functioning at baseline are most likely to benefit from physical activity interventions.[20,21]

Physical Activity and Physiological Outcomes in Cancer Survivors

Randomized clinical trials demonstrate that physical activity interventions improve a variety of important physiological outcomes, such as cardiorespiratory fitness, muscle strength, and body composition, in cancer survivors. A systematic review and meta-analysis 48 of randomized controlled trials including 3,632 individuals (21 studies examined stage I-III breast cancer) demonstrated that aerobic physical activity significantly increased cardiorespiratory fitness (Weighted Mean Difference (WMD): 2.13 $mL \cdot O_2 \cdot min$; 95% CI: 1.58 to 2.67) before, during, and after the completion of cancer treatment.[22] An individual patient data meta-analysis of 28 studies including 3,515 individuals (67% of study participants with stage I-III breast cancer) demonstrated that strength based physical activity increases upper-body (SMD: 0.20; 95% CI: 0.14 to 0.26) and lower-body (SMD: 0.29; 95% CI: 0.23 to 0.35) muscle strength, with supervised physical activity inducing larger improvements compared to unsupervised activity.[21] Emerging evidence also suggests physical activity improves objective measures of body composition in cancer survivors. In a meta-analysis of eight studies with 713 individuals, muscle strengthening activities reduced body fat percentage (WMD: −2.1; 95% CI: −3.5 to −0.70) and increased lean body mass (WMD: 1.07; 95% CI: 0.8 to 1.4) compared to control.[23]

Physical Activity Guidelines for Everyone, Cancer Survivors Too

In 2018, the Department of Health and Human Services released the second edition of the Physical Activity Guidelines for Americans.[24] Included here are key recommendations that are applicable to all Americans, including cancer survivors:

1. Sit less during the day. Some physical activity is better than no physical activity. Avoid prolonged periods of physical inactivity. Individuals who sit less and do any physical activity gain some health benefits when compared to individuals who do no activity at all.
2. For considerable improvements in health, accrue ≥150 minutes of moderate-intensity, or ≥75 minutes of vigorous-intensity aerobic physical activity each week. Aerobic physical activity should be spread throughout the week if feasible.
3. Because of chronic conditions, when 150 minutes of moderate-intensity aerobic physical activity each week cannot be accrued, be as physically active as abilities and conditions permit.
4. By accruing ≥300 minutes of moderate-intensity physical activity each week additional health benefits are gained.
5. Resistance and muscle strengthening physical activities offer additional health benefits that are unique to the health benefits of aerobic physical activities.
6. Older adults and those at risk for functional limitations should also perform balance and flexibility activities on days that other physical activity is performed (e.g., stretching prior to aerobic physical activity).

Multiple organizations including the American College of Sports Medicine,[25] American Cancer Society,[26] National Comprehensive Cancer Network,[27] and other international exercise and oncology groups[28,29] have endorsed similar guidelines for exercise prescription in cancer survivors. These guidelines also provide some guidance regarding individualization of physical activity programs in the setting of side effects of cancer treatment (e.g., neuropathy, bone metastases, etc.) to maximize the efficacy and minimize adverse effects, but evidence remains limited.[30]

In addition to physical activity to optimize health and wellness, the American Cancer Society and National Comprehensive Cancer Network recommend that cancer survivors achieve and maintain a healthy weight throughout life (e.g., avoid excess weight gain at all ages), eat a healthy diet with an emphasis on plant foods (e.g., limiting how much processed meat and red meat consumed, consuming ≥2.5 cups of fruits and vegetables each day, choosing whole grains instead of refined grain products), and limit alcohol intake (e.g., ≤1 drink per day for women or ≤2 per day for men).[26,31]

Putting Exercise into Oncology Practice

Despite the observation that one minute of moderate-intensity physical activity is associated with seven minutes of additional life,[32] less than one-fifth of the adult population are aware that national guidelines recommend participation in physical activity,[33] and survey studies of

self-reported lifestyle behaviors suggests that less than one-third of cancer survivors meet the recommended weekly volume of physical activity.[34] Given the established health benefits of physical activity, this modality is uniquely positioned as a therapy that may improve both the quality and duration of life after cancer diagnosis.

Oncologists should provide evidence-based recommendations to cancer survivors. Many cancer survivors will seek to understand how to become more physically active and what health benefits they can expect to achieve.[35] Oncologists can provide patients with educational materials to ensure that survivors have the basic information about physical activity recommendations.[36] Oncologists may also consider referring patients to community-based physical activity programs, such as LIVESTRONG at the YMCA. A randomized controlled trial demonstrated that the LIVESTRONG program safely increases physical activity, physical fitness capacity, and improves quality of life in a heterogeneous sample of cancer survivors.[37] LIVESTRONG at the YMCA is currently offered at 735 branches, making it the most widely available structured evidence-based physical activity program designed specifically for cancer survivors in the United States. For cancer survivors who seek individualized physical activity training, the American College of Sports Medicine created a subspecialty certification to enable qualified personal trainers to provide physical activity counseling to cancer survivors. Local personal trainers who are cancer certified can be identified by patients or their physicians on the Find a Pro website (https://bit.ly/2NcESr1).

Beyond community-based and individualized personal training programs, developing efficacious and scalable strategies to promote physical activity to the 15 million cancer survivors in the United States has been challenging. In a systematic review and meta-analysis of 19 randomized controlled trials, interventions that integrated an array of behavior change techniques, such as goal setting, problem solving, and self-monitoring, only modestly increased volume of moderate- to vigorous-intensity physical activity (SMD: 0.25; 95% CI: 0.16 to 0.35), a between group increase of approximately 38 minutes each week.[38] Interventions that were more successful promoting physical activity included more contacts with patients and contained supervised elements. It is noteworthy that few of these interventions were able to sustain long term changes in physical activity,[39,40] which will be of critical importance to promote sustained health benefits in cancer survivors. Most of these studies are biased towards the inclusion of younger, female, well-educated, and Caucasian populations of breast cancer survivors who already engaged in modest amounts of physical activity.[38] This is a critical issue because cultural, geographic, and social factors influence health behaviors, including physical activity, and possibly serve as a barrier to widespread adoption of physical activity.[41,42]

Future research documenting the health benefits of physical activity for cancer survivors across diverse cultural, geographic, social and economic environments will help to establish and solidify the importance of this treatment modality in oncology care globally.[43] Lastly, greater attention to how these physical activity interventions fit into the clinical oncology workflow and the electronic health record are necessary. Most oncologists value the importance of healthy lifestyle such as physical activity and encourage their patients to become more physically active, but referral to personal trainers and community-based

programs to support increased physical activity was infrequent and accompanied by numerous barriers.[44]

Conclusions

Over the past three decades a voluminous evidence base has been established that supports physical activity providing cancer survivors with myriad health benefits. Observational studies have consistently reported an association between participation in physical activity after a diagnosis of cancer and a lower risk of disease recurrence and cancer specific mortality. Translational studies using biomarker endpoints support the biologic plausibility of this relationship as possibly being causal. Ongoing multi-center phase III randomized clinical trials will offer definitive evidence regarding the benefits of physical activity to improve clinical outcomes in cancer survivors. Physical activity consistently improves a variety of patient reported outcomes including quality of life and physiological outcomes related to physical health and wellness. Numerous organizations have published guidelines for physical activity in cancer survivors, and these guidelines can be summarized in four words: sit less & move more. However, translating this robust and provocative evidence base into clinical practice has been challenging. Future studies are necessary to determine how best to promote physical activity in cancer survivors within the constraints of a busy oncology workflow, segregated healthcare systems, and heterogenous patient populations. This next frontier of studies will have an important role in accelerating the translation of evidence-based discoveries into the clinic and establishing physical activity as an integral part of cancer care.

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