Exercise Therapy and Cardiovascular Benefits in Patients with Cancer

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Amy M. Berkman and Susan C. Gilchrist

Abstract
Exercise therapy improves vascular function and survival. In this chapter we briefly review the benefits of exercise therapy in patients with cancer.

Keywords
Exercise therapy • Cardiovascular • Cancer

Introduction

Common treatments for cancer, such as molecular targeted therapies, radiation, and particular chemotherapeutic agents are known to directly contribute to structural heart disease, vascular compromise, and systolic heart failure [1]. In addition, cardiovascular disease (CVD) risk factors, such as body weight, blood pressure, and cardiorespiratory fitness (CRF) worsen in cancer patients post-treatment, compared to pre-diagnosis risk factor burden [2, 3]. Medical therapies, such as aspirin or anticoagulants to prevent or treat thrombotic risk [4] statins, angiotensin-converting enzyme (ACE) inhibitors, or beta-blockers to treat cancer patients who have left ventricular (LV) dysfunction [5, 6]; and protective therapies, such as dexrazoxane, specifically aimed at preventing anthracycline induced cardiotoxicity [7], are currently used to offset cancer related insults to the cardiovascular system. However, the timing of CVD events in cancer patients is unpredictable and can occur years after a cancer diagnosis and treatment, making the timing and choice of medical therapies challenging.

A.M. Berkman
University of Vermont School of Medicine, University of Vermont, Burlington, VT, USA

S.C. Gilchrist (✉)
Department of Clinical Cancer Prevention and Cardiology, The University of Texas M.D. Anderson Cancer Center, 1155 Pressler, Houston, TX 77006, USA
e-mail: sgilchrist@mdanderson.org

The potential of non-medical therapy, particularly exercise training, is receiving increasing attention as a safe and effective way to mitigate the cardiovascular effects of cancer treatment, as well as promote future all-around health. In non-cancer populations, exercise training has already been shown to reduce recurrent myocardial infarction, improve survival among patients with coronary artery disease, improve LV function, and reduce the risk of stroke [8–12]. In addition, aerobic exercise training has proven to be an effective means of inducing weight loss, decreasing the risk of hypertension, and improving CRF [13–15]. While exercise training has not been studied as extensively in the cancer population, data are promising, with exercise training shown to significantly improve vascular function [16, 17], skeletal muscle function [18, 19], and maintain or improve CRF in cancer patients [19–23], a key predictor of survival [24–28].

Assessment of CRF Prior to Exercise Training in Cancer Patients

Given the role for exercise training to improve the cardiovascular health of cancer patients, it is important to implement standardized clinical measurements and practices across the cancer care spectrum. A good starting point is the measurement of CRF. CRF is an objective measurement of response to aerobic exercise training, as well as a marker of accelerated cardiac aging experienced during cancer treatment, and, importantly, prognostic of survival before and after a cancer

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diagnosis [20, 29]. Measurement of CRF (VO_{2peak}), via cardiopulmonary exercise testing (CPET), is clinically feasible and established in the cancer setting [30]. CPET is a non-invasive test performed on a treadmill or stationary bike that measures both gas exchange (requiring a mouthpiece or facemask) and cardiac (ECG) monitoring. Uniquely, it can simultaneously assess multiple organ systems (cardiac, skeletal muscle, pulmonary) impacted by cancer treatment. Additionally, CPET can help clinicians make decisions regarding cardiopulmonary readiness for an exercise training regimen, as well as inform individually tailored exercise prescriptions for cancer patients. A CPET should be performed to make sure that cancer patients participate in aerobic exercise from a cardiopulmonary standpoint and in order to assess current CRF level and heart rate response to exercise. Importantly, exercise intensity recommendations are based on a percent of VO_{2peak} attained during CPET. After cardiopulmonary readiness has been assessed, opportunities to incorporate exercise training in the cancer setting to improve CRF and mitigate decline of cardiac health can be initiated. Below are several case examples of exercise training across different points in the cancer continuum.

Case Examples of Exercise Training in the Cancer Setting

Post Diagnosis/Prior to Surgery

Exercise training prior to surgery (prehabilitation) provides an opportunity to mitigate loss of CRF and enhance functional capacity prior to surgery [31]. A recent systematic review of 18 exercise training trials among 966 cancer patients provides supportive evidence of its effectiveness. A typical patient and exercise prescription are as follows: a 65 year old man presents with stage T2 nonsmall-cell lung cancer. He is a former smoker and is currently overweight with a BMI of 27 kg/m^2 and CRF (VO_{2peak}) of 15.7 mL/kg/min, which is lower than expected for his age. A 5-week exercise prescription, either on cycle ergometer or treadmill, is recommended prior to surgery. The patient is told to exercise 5 days for 20 min each day at an intensity of 60% of VO_{2peak} during the first week of exercise training (Of note, intensity is determined by the patient's peak heart rate (PHR) during CPET, given heart rate is linearly related to VO_2 (40%–85% of VO_{2peak} is equivalent to 50%–90% of PHR)). On weeks 2 and 3 he should continue to exercise 5 days out of the week for 20–25 min sessions and at 60–65% VO_{2peak} On weeks 4 and 5 the patients will perform 3–4 sessions/week at 60–65% VO_{2peak} for 25–30 min as well as 1–2 session/week of interval training (30 s at peak VO_2 followed by active recovery for 60 s with a total of 10–15 intervals). Under this exercise training regimen, the patient can be expected to increase his CRF by 3.3 mL/kg/min, which is a clinically significant change in CRF [32].

During Active Treatment

Based on a systematic review and meta-analysis by Schmitz et al., there is weak evidence for exercise interventions to improve CRF during active treatment in breast cancer [33]. However, the weight of the evidence does suggest that exercise mitigates loss of CRF during active treatment. For example, a 50 year old female breast cancer patient with a BMI of 26.5 kg/m^2 and a VO_{2peak} of 29 mL/kg/min, assessed by CPET, who exercises at the Physical Activity Guidelines for Americans recommended 75 min/week of vigorous aerobic exercise or 150 min/week of moderate aerobic exercise can expect to lose 12% of her CRF over 16 weeks of breast cancer treatment. For this patient, an exercise regimen that can successfully mitigate this fitness loss is as follows: 50–60 min sessions 3 times/week on either a cycle or rowing ergometer, treadmill, or elliptical; weeks 1 and 2 sessions should be performed at an intensity of 55–60% VO_{2peak}, weeks 3 and 4 sessions should be performed at 60–65% VO_{2peak}, weeks 5 and 6 sessions should be performed at 65–70% VO_{2peak}, and remaining weeks 7–16 sessions should be performed at 70–75% VO_{2peak} Following this exercise training prescription, the patient can expect to only lose 9% of her CRF, which is an improvement over the expected loss [21]. This is important given the loss of CRF experienced during active treatment can be substantial (~30%) [29]; as such, maintaining CRF during treatment has the potential to promote quicker recovery and improvement in CRF in the post-treatment setting.

Post Treatment

The benefits of exercise training in the post-treatment setting on CRF have been demonstrated in multiple cancer types. Based on a meta-analysis of randomized controlled trials, a pooled increased in VO_{2peak} of 2.2 mL/kg/min ($p < 0.01$) has been demonstrated among cancer survivors including breast, colorectal, prostate, lung, and lymphoma malignancies [34]. Exercise training post treatment is performed with the goal of getting a patient back to their pre-diagnosis CRF level. This is important regardless of age or cancer diagnosis, but may be particularly important among survivors of childhood cancer who are eager to get back to the pre-diagnosis school and community activities. For example, a 16 year old male survivor of childhood acute lymphoblastic leukemia presents with a BMI of 25.1 kg/m^2 and a VO_{2peak} of 35.2 mL/kg/min. For this patient, a 16 week, home-based exercise training regimen is prescribed, which consists of both strength training and aerobic activity. The strength training prescription includes resistance exercises that target all major muscle groups and should be completed 3–4 times/week. Aerobic exercise, consisting of brisk walking, jogging, or sports, should be undertaken at least three times a week for at least 30 min/session. After completing 16 weeks of training, the patient on average will significantly increase his CRF by 5.4 mL/kg/min [35].

Conclusion

Exercise is a non-pharmacologic strategy to mitigate cardiac insult and promote improvement in CRF across the cancer continuum. We recommend use of CPET prior to exercise training to (1) provide an objective assessment of cardiopulmonary health, (2) determine feasibility to perform exercise training, and (3) provide objective data and exercise goals for patients, oncologists, primary care physicians and others in health care field invested in a cancer patient's recovery. CPET also offers a level platform to begin cancer rehabilitation, specifically aerobic exercise, independent of the cancer rehabilitation model chosen to be cost-effective and feasible across institutions and communities. Integrating this message and delivering personalized exercise prescriptions to patients in the cancer setting should be a priority in cancer care, especially given the impact of exercise training on CRF, as illustrated in the cases above. Ultimately, exercise should be promoted and maintained across all facets of the cancer continuum, including the preventative setting.

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