# Safeguarding Exercise Capacity Throughout and After Cancer Treatment

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## Introduction

Advances in early detection and treatment have improved survival rates of cancer over the past decades, with approximately 60% of patients living more than 5 years after diagnosis. Despite this longevity, cancer and its treatment are often associated with physical and psychosocial side effects, i.e. both long-term effects present during treatment and persisting afterwards, and late effects, which did not occur during treatment but appear later. In the process of destroying cancer cells, radiation therapy and chemotherapy also cause alterations to normal tissue and body functions, resulting in toxicities in many organs and body systems. Also, hormonal therapies such as androgen and oestrogen suppression, while highly effective for treating prostate and breast cancer, respectively, cause considerable side effects. While controlling the cancer, there is significant impact on the patient, including the cardiovascular, pulmonary, gastrointestinal, (neuro)endocrine, immune, and musculoskeletal systems. As a consequence, cancer survivors[a] experience reduced cardiorespiratory fitness, reduced muscle mass and strength, increased

[a]The Centers for Disease Control and Prevention defined a cancer survivor as anyone who has been diagnosed with cancer, from the time of diagnosis through the rest of life.

fat mass, reduced bone health, and fatigue. Furthermore, many cancer survivors are at increased risk for anxiety, depression, sleep disturbances, reduced self-esteem, and lymphoedema. These adverse long-term and late effects severely impact the patient's quality of life (QoL).

## Reduced Cardiorespiratory Fitness

Cardiorespiratory fitness is determined by the transport of oxygen from the environment to skeletal muscles via several components of the pulmonary and cardiovascular systems including blood and blood vessels and by the capacity of skeletal muscle to utilise this oxygen. Cancer and its treatment may affect cardiorespiratory fitness via several mechanisms. For example, pulmonary mechanics and gas exchange may be disrupted by a tumour in the lungs, and anaemia may reduce the oxygen-carrying capacity. Systemic therapy may result in cardiac limitations. For example, anthracyclines could lead to atrial and ventricular arrhythmias, pericarditis, myocarditis, a reduced ejection fraction, and cardiomyopathy. Alkylating agents such as cisplatin may result in myocardial ischaemia/infarction, hypertension, heart failure, and arrhythmias. Chemotherapeutic agents may also reduce the muscle capacity for oxygen utilisation. Furthermore, radiotherapy in the chest area might cause cardiac or pulmonary limitations, such as angina, dyspnoea, heart failure, pericardial constriction, atherosclerosis, and mediastinal fibrosis, and may cause localised damage to muscle agents. In addition, androgen-suppression therapy results in considerable changes to the quantity and quality of skeletal muscle. Finally, low cardiorespiratory fitness levels may also result from reduced physical activity after cancer diagnosis, leading to a reduction in cardiac output, oxidative capacity, and muscle cross-sectional area.

The best direct measurement of cardiorespiratory fitness is the peak oxygen uptake (peak$VO_2$). A review by Steins Bisschop and colleagues showed that most studies of cancer survivors reported reduced peak$VO_2$ levels (between 16 and 25 mL/min/kg). Lower peak$VO_2$ values in cancer survivors compared to the healthy population indicate decreased cardiorespiratory fitness levels and, consequently, are an indication for physical exercise training. Moreover, screening for cardiac, pulmonary, or musculoskeletal limitations before the start of an exercise programme is recommended. Low peak$VO_2$ has also been shown to be related to an increased risk of premature death.

Peak$VO_2$ can be measured during a cardiopulmonary exercise test (CPET) with continuous gas exchange analysis during incremental exercise, which is generally conducted on a cycle ergometer or treadmill and is considered feasible and safe. It can be used to monitor individual cardiorespiratory fitness and allows exercise programmes to be tailored to individual fitness levels by using either a percentage of peak$VO_2$, a percentage of the peak heart rate, or the heart rate at the anaerobic threshold to guide exercise intensity.

Exercise during or after cytotoxic cancer treatment was found to be associated with significant improvements in peak$VO_2$ compared to a non-exercise control group. Larger improvements were found in patients who participated in an exercise programme after completion of cancer treatment. This suggests that exercise during adjuvant therapy is of primary importance to maintain cardiorespiratory fitness.

## Reduced Muscle Mass and Strength

Muscle wasting is present in approximately 50% of cancer survivors, contributing to decreased responsiveness to cancer treatment and severe dose-limiting toxicities, in turn contributing to poor prognosis and increased morbidity and mortality. Because muscle strength is related to muscle mass, muscle wasting also contributes to weakness and reduced functional ability and independence. In addition, due to its mediating role, muscle wasting may have serious consequences on glucose metabolism and chronic low-level systemic inflammation. Muscle wasting results from an imbalance between the rate of muscle protein synthesis and degradation and, in particular, from accelerated muscle protein degradation. Mechanisms underlying muscle protein degradation include tumour- and treatment-related increases in pro-inflammatory cytokines and proteolysis-inducing factors, as well as testosterone suppression, reduced food intake, and low physical activity levels.

## Increased Fat Mass

Cancer and its treatment are commonly associated with changes in body composition. The specific detrimental changes in total weight, lean body mass, and fat mass differ by cancer and treatment types. An increase in fat mass is common during adjuvant treatments, for example for breast, colon, prostate, and gynaecological cancer, which has a significant impact on the risk of type 2 diabetes, asthma, chronic back pain, osteoarthritis, metabolic syndrome, and cardiovascular disease. In addition, obesity has been associated with a poorer overall and cancer-specific survival.

## Reduced Bone Health

Hypogonadism and the subsequent oestrogen deficiency associated with cancer treatment (chemotherapy, hormone therapy) can result in an imbalance between function of the osteoblasts and osteoclasts, resulting in greater bone resorption than formation. The result is a net loss of bone density and an increased fracture risk. Patients with breast or prostate cancer in particular are at increased risk for reduced bone health. Premenopausal women who are treated with alkalytic agents are at increased risk for cessation of ovarian function, which reduces oestrogen levels. Also, men treated with androgen-suppression therapy experience a decrease in oestrogen that parallels the reduction in testosterone. Furthermore, a high incidence of osteopenia and osteoporosis is observed in long-term survivors of Hodgkin's and non-Hodgkin's lymphoma treated with stem cell transplantation.

## Exercise as Medicine in the Management of Cancer

Several reviews and meta-analyses demonstrate beneficial effects of physical activity and exercise[b] in cancer survivors during and after treatment on physical and psychosocial outcomes. These include increased cardiorespiratory fitness, muscle mass and strength, reduced fatigue and depression, and improved QoL. The Physical Activity across the Cancer Continuum (PACC) framework proposes four time periods following

[b]Exercise is a specific type of physical activity that is planned, structured, and repetitive and aims to improve or maintain physical fitness, performance, or health.

diagnosis during which physical activity can have an important role: pre-treatment, during treatment, survivorship, and end-of-life care.

The aim of exercise pre-treatment is to improve physical fitness (including cardiorespiratory fitness and muscle strength) prior to surgery or systemic therapy to enable patients to undergo treatment with fewer side effects or to enhance post-treatment recovery. In a systematic review of randomised controlled trials (RCTs) and non-RCTs, Singh and colleagues reported that the data available from patients with lung cancer, prostate cancer, and cancer of the abdominal area (e.g. colon, colorectal, liver) suggest that exercise – aerobic, resistance, or pelvic floor training alone or in combination – may have a positive effect on rate and duration of continence, functional walking capacity, and cardiorespiratory fitness. Some studies reported improved QoL and reduced length of hospital stay (which is an important prognostic variable for a positive surgical outcome), but findings were inconsistent, likely due to lack of power and differences in training duration prior to surgery.

In a meta-analysis by Speck and colleagues, results of exercise during and after cancer treatment were presented separately. During treatment, small to moderate significant effects of exercise were reported for cardiorespiratory fitness, upper and lower body muscle strength, body weight, functional QoL, anxiety, and self-esteem. After treatment, large significant effects were found for upper and lower body muscle strength and breast cancer-specific concerns, and small to moderate significant effects for physical activity level, cardiorespiratory fitness, overall QoL, fatigue, insulin-like growth factor-1 (IGF-1), and symptoms and side effects. Similar effects were reported in other meta-analyses on this topic.

Resistance exercise is a potent stimulus of muscle synthesis, and consequently increasing muscle mass, endurance, and strength, thereby improving physical function and QoL. Exercise (aerobic, resistance, or a combination of both) during cancer treatment can improve upper and lower body muscle strength more than usual care. In a recent meta-analysis of RCTs evaluating the effects of resistance exercise during and after cancer treatment, Strasser and colleagues reported a significant increase in lower and upper body muscle strength and lean body mass.

Improvements in lower body muscle strength were greater in cancer survivors who completed an exercise intervention after cancer treatment, compared to those who exercised during cancer treatment. Whether there is a dose–response relationship remains unclear; however, the results suggest that exercise volume may be more important than exercise intensity in order to induce muscle protein synthesis.

Exercise and, in particular, resistance training and high-impact loading exercise can positively influence bone health by its osteogenic effects. Resistance exercises should be performed at sufficient intensity and should specifically load a target bone, thus both the hips and the spine. Weight-bearing activities such as jumping and skipping are more osteogenic than activities with lower impact forces; however, aerobic exercises using upper and lower body muscles and/or trunk rotation at sufficient intensity, such as aerobic dance, may also benefit patients with osteogenesis. Walking interventions generally have limited effect on bone health because the relatively low ground reaction force does not reach sufficient intensity to augment bone density.

The relative benefit of exercise versus pharmacological treatment is yet to be determined. Although exercise can be an effective non-pharmacological strategy for preserving bone health during and after cancer treatment, adequate calcium and vitamin D supplementation and treatment with pharmacological agents such as bisphosphonate and RANK-ligand monoclonal antibody may also be important. These agents are, however, associated with considerable side effects.

Few studies have examined the effects of physical activity in palliative cancer patients. The few case reports and uncontrolled trials available suggest that the role for physical activity is promising, as it may maintain physical function, independence in activities of daily living, and overall QoL. It is therefore recommended to encourage palliative cancer patients to consider a physical activity intervention under the specific direction and guidance of their attending medical team.

## Physical Activity and Cancer Outcome

Sufficient levels of physical activity may also be important to improve disease-free and overall survival. Observational studies showed that higher levels of moderate-to-vigorous physical activity were associated with lower mortality risk in survivors of breast, colon, and prostate cancer, with physically active survivors having approximately 50% lower mortality. However, to establish a causal relationship between physical activity and survival, additional RCTs are needed.

RCTs evaluating the effects of physical activity on biomarkers related to cancer prognosis have recently been summarised by Ballard-Barbash and colleagues. The results suggest that exercise may result in beneficial changes in circulating levels of insulin, IGF-1, and IGF-1 binding proteins in breast cancer survivors. There is also evidence that exercise leads to beneficial changes in circulating levels of C-reactive protein and in natural killer cell cytotoxic activity in cancer survivors, including breast, prostate, and gastric cancer. In prostate cancer survivors, there is consistent evidence that exercise does not increase prostate-specific antigen (PSA) or testosterone levels. Evidence for other biomarkers is limited or non-existent. Also, the mediating role of immune, endocrine, or musculoskeletal systems on the effects of exercise on cancer outcomes requires further investigation.

Furthermore, the interaction between physical activity and primary cancer treatment remains unclear. In the START trial, Courneya and colleagues found chemotherapy completion rates to be higher in patients who completed a resistance exercise programme during adjuvant chemotherapy treatment for breast cancer (89.8%), compared to a usual care control group (84.1%) or an aerobic exercise group (87.4%). This resulted in higher survival rates among the exercise groups compared to the control group.

In addition to observational data on survival and experimental data on biomarkers in cancer survivors, a few studies in animals suggested that exercise may inhibit tumour growth, but others did not. At present, further investigation on the effects of physical activity on chemotherapy completion rates and tumour growth is needed.

## Physical Activity Guidelines

Given the increasing number of studies showing the safety and benefits of physical activity, exercise should be part of the standard care for all cancer survivors. Several evidence-based physical activity guidelines for cancer survivors have been published.

In 2010, the American College of Sports Medicine (ACSM) published physical activity guidelines for cancer survivors, which were based on extensive systematic review of the literature on adult survivors of breast, prostate, colon, haematological, and gynaecological cancers. The expert panel reported consistent evidence regarding the safety of exercise during and after cancer treatment (including intensive treatments such as bone marrow transplant) and beneficial effects on cardiorespiratory fitness, muscle strength, QoL, and fatigue. The ACSM recommends that cancer survivors should be as physically active as their abilities and conditions allow. Importantly, the recommendation is that cancer survivors should avoid being physically inactive regardless of cancer stage or treatment. Adult cancer survivors are advised to engage in either at least 150 minutes per week of moderate intensity or 75 minutes per week of vigorous intensity aerobic physical activity, or an equivalent combination of both. Muscle-strengthening activities involving all major muscle groups are recommended at least two sessions per week. Several precautions for exercise should be taken into account, including arm and shoulder problems, skeletal fractures, infection risk, ostomy, and swelling or inflammation in the abdomen, groin, or lower extremity.

Lymphoedema is not a contraindication to exercise. A recent RCT showed that women with breast cancer-related lymphoedema can safely lift heavy weights during upper body resistance exercise, without fear of lymphoedema exacerbation or increased symptom severity.

Comparable physical activity guidelines have been published by the American Cancer Society (ACS), Exercise and Sport Science Australia, Comprehensive Cancer Center the Netherlands, the German Cancer Association, and the British Association of Sport and Exercise Science.

Current physical activity guidelines for cancer survivors are rather generic. Additional research is needed in order to develop more specific guidelines for a given exercise prescription (e.g. mode, frequency, intensity, duration), for a given cancer site at a particular phase of the cancer trajectory, and for specific outcomes. Future studies should focus on identifying clinical, personal, physical, psychosocial, and intervention moderators explaining "for whom" or "under what circumstances" interventions work. In addition, more insight into the working mechanisms of exercise interventions on health outcomes in cancer survivors is needed to improve the efficacy and efficiency of interventions. Existing programmes should also embrace the interests and preferences of patients to facilitate optimal uptake of interventions, and must take the principles of exercise training into account.

Declaration of Interest:

Dr Buffart has reported no conflicts of interest.

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## Further Reading

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