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Exercise and cancer

Eser Prisca, Wilhelm Matthias

Department of Cardiology, Interdisciplinary Centre for Sports and Exercise Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland

Summary

Evidence for the effectiveness of exercise to improve physical functioning, body composition, fatigue and quality of life in cancer patients is promising and, in general, exercise is safe and feasible throughout the course of cancer care.

Keywords: cardiotoxicity, exercise, cancer, sports medicine

Epidemiology of cancer

A growing and aging population, along with improved cancer survival rates, are both contributing to increasing cancer prevalence. Today approximately 300,000 cancer patients are living in Switzerland, amounting to double the number of 25 years ago. More than half of all new cancer cases are caused by four cancer types: breast (women), prostrate (men), lung and colorectal cancer (both sexes). After cardiovascular disease (CVD), cancer is the second leading cause of death in Switzerland, and the leading cause of death in the age group of 45 to 84 years in both women and men [1].

Shared risk factors of cancer and cardiovascular diseases

Although commonly thought of as two separate disease entities, CVD and cancer possess various similarities and possible interactions, including a number of similar risk factors (table 1). Emerging evidence suggests a shared biology [2]. Moreover, patients who develop cancer are at risk for a sedentary lifestyle due to cancer-related exercise intolerance and suboptimal CVD prevention. The addition of cardiotoxic radio- and/or chemotherapies contribute to an even higher CVD risk (fig. 1). Particularly for breast cancer, this has been acknowledged in a recent scientific statement of the American Heart Association [3]. In long-term cancer survivors, CVD has become a leading cause of death, beside cancer recurrences and other cancers [4].

Cardiovascular complications of cancer therapy

Different chemotherapeutic agents, alone or in combination with radiotherapy, may lead to the development of CVD (myocardial dysfunction, heart failure, coronary artery disease, valvular heart disease, arrhythmias, arterial hypertension, thromboembolic disease, peripheral vascular disease or stroke) [5]. As an example, anthracycline regimens are widely used in protocols for breast cancer, sarcoma, lymphoma and paediatric leukaemia. They cause dose-dependent and progressive cardiac damage, clinically manifest as decreased left ventricular function, which in severe cases leads to heart failure and ventricular arrhythmias. The incidence of heart failure increases dose- and compound-dependent, for example with doxorubicin from 3–5% (400 mg/m^2) to 18–48% (700 mg/m^2) [5].

Exercise intolerance in cancer patients

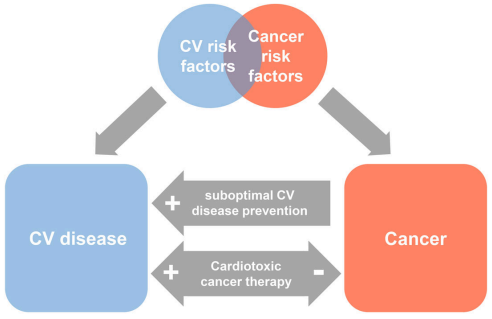
The aetiology of exercise intolerance in cancer patients is multifactorial. Patient-specific limitations, such as age and comorbidities, interact with disease-specific limitations, such as type of surgery, and chemo-, radio-, or hormone therapies. All may affect oxygen uptake, transport

Table 1: Modifiable cardiovascular health and risk factors with their estimated risk for the four most common cancers.

	Breast	Prostate	Lung	Colorectal
Physical activity	▼			▼▼ (colon)
Unhealthy diet	▲			▲▲
Obesity	▲▲			▲ (w) ▲▲▲(m)
Diabetes	▲▲			▲▲
Hypertension			▲	▲
Tobacco smoking	▲	▲▲	▲▲▲	

w = women; m = men. Hazard ratios (HR): ▼▼ HR 0.6–0.79, ▼ HR 0.80–0.99, ▲ HR 1.01–1.19, ▲▲ HR 1.20–1.39, ▲▲▲ HR ≥1.40, adapted from [2, 3].

Figure 1: Shared risk factors and the development of cardiovascular diseases in cancer patients.



Correspondence:
Prof. Matthias Wilhelm, MD, Department of Cardiology, Interdisciplinary Centre for Sports and Exercise Medicine, Bern University Hospital, University of Bern, CH-3010 Bern, matthias.wilhelm[at]insel.ch

and utilisation, leading to or aggravating muscular deconditioning [6]. Beside this biological view of exercise intolerance, psychosocial aspects also have to be considered. The ability to exercise may be impaired because of cancer-related pain or fatigue. Symptoms of anxiety or depression may curb or abolish the desire and motivation to exercise. In addition, lack of time, insufficient social support, a negative attitude towards exercise and the lack of perceived benefits from exercise are other barriers towards participation in regular exercise [7]. Depending on the degree and duration of inactivity, exercise intolerance may develop, and a vicious circle of physical deconditioning, fatigue and inability to exercise may develop, all-in-all negatively affecting quality of life and CVD risk. In analogy to heart failure, exercise intolerance in cancer patients can be successfully tackled by the application of exercise training. There is still a prevailing clinical mind-set that the development of symptoms such as breathlessness and muscular fatigue indicates that exercise may be adverse to the patient's physical condition. Instead, we need to consider that such symptoms are needed for the signalling between the periphery and central haemodynamic performance and that regular physical activity will ultimately lead to favourable changes in symptoms and functional capacity [8].

Exercise as important adjuvant therapy at all stages of the cancer care pathway

Observational studies, interventional trials, and meta-analyses support the view that exercise is an important adjunct therapy from pre-treatment to the survivorship stage (health promotion) or palliative care (quality of life). Specifically, there is preliminary or promising evidence that cancer patients involved in higher levels of exercise have a lower relative risk of cancer mortality, a lower relative risk of cancer recurrence, and experience fewer and/or less severe treatment-related adverse effects (table 2) [9, 10].

Table 2: Evidence for the impact of exercise on different outcomes at different cancer stages.

	Breast	Prostate	Lung	Colorectal
Exercise during cancer treatment				
Physical function	●●	●	●	●
Fatigue	●●	●/●●	●●	●●
Quality of life	●	●	●	●
Exercise after cancer treatment				
Physical function	●/●●	●●	●●	●●
Body composition	●	●	●	●
Fatigue	●/●●	●●	●●	●●
Quality of life	●	●	●	●
Cancer recurrence	●	●		●
Survival	●	●	●	●
Exercise during palliative care				
Physical function	●	●	●	●
Body composition	●	●	●	●
Fatigue	●	●	●	●
Quality of life	●	●	●	●

Level of evidence: ● Preliminary – low quality of evidence with considerable uncertainty over the effects demonstrated. ●● Promising – moderate quality body of evidence with some uncertainty over the effects demonstrated. Adapted from [9].

Modulation of cardiotoxicity by aerobic exercise

The evidence for the effectiveness of exercise to improve physical functioning, body composition, fatigue and quality of life in cancer patients is promising, but the evidence for the efficacy of exercise to prevent or mitigate cardiovascular toxicity is limited [11]. However, for selected compounds such as anthracyclines, the underlying mechanisms of cardiotoxicity and the potential of aerobic exercise for prevention and treatment have been studied in animals. Anthracycline-induced oxidative injury accelerates cardiac myofilament apoptosis, suppresses protein synthesis, leads to ultrastructural changes and impairs mitochondrial energy metabolism. These alterations ultimately lead to myocardial dysfunction and heart failure. Aerobic exercise interventions may modulate anthracycline-induced cardiotoxicity by mitigating oxidative stress, apoptosis and ultrastructural changes, and improving protein synthesis and mitochondrial energy metabolism [12]. More recently, studies in humans have been instigated to assess the transferability of the positive results from animal studies. A conceptual research framework has been proposed to facilitate personalised risk assessment and the development of targeted exercise prescriptions to optimally prevent or manage cardiovascular toxicity after a cancer diagnosis [11]. In 2019, the Inselspital Bern launched a study in breast cancer patients funded by the Swiss Cancer League to test the hypothesis that anthracycline-mediated cardiotoxicity can be alleviated with a personalised exercise training programme (Cancer Adverse effects PReventIon with Care & Exercise: the CAPRICE study, NCT03850171).

Exercise recommendations for cancer patients

In 2009, the American College for Sports Medicine (ACSM) published a consensus statement on exercise for cancer patients [13]. These guidelines were developed against the backdrop of existing recommendations for exercise from the ACSM and the American Heart Association, and the 2008 US Department of Health and Human Services (US DHHS) Physical Activity Guidelines for Americans. The latter were updated recently [14]. All of these guidelines are similar, with minor variations. The recent US DHHS guidelines indicate that, when individuals with chronic conditions such as cancer are unable to meet the stated recommendation because of their poor health status, they "should be as physically active as their abilities and conditions allow." An explicit recommendation was made to "avoid inactivity", and it was clearly stated that "some physical activity is better than none." The key US DHHS guideline for aerobic activity focused on an overall volume of weekly activity of 150 to 300 min of moderate-intensity exercise or 75 to 150 min of vigorous-intensity exercise or an equivalent combination. Guidance for strength training is to perform at least two weekly sessions that include exercises for major muscle groups [14].

Implementation of exercise training

Exercise programmes of supervised training achieves higher fitness levels than unsupervised training [15]. Exercise training has to be personalised, based on cancer stage,

patients' preferences and abilities [11]. Before treatment, during treatment (phase I) and early after treatment (phase II) it can be integrated in comprehensive cancer rehabilitation programmes. Programmes should implement concepts for long-term adherence (phase III) to individual exercise training, both for cancer survivors and in palliative situations [9]. The "National Cancer Strategy 2014-2017" highlighted the importance of cancer rehabilitation [16]. However, in Switzerland, cancer rehabilitation is currently not covered by the compulsory health insurance, unlike cardiac rehabilitation. Initiatives from https://oncoreha.ch and the Swiss Cancer League are on the way. In clinical practice, ambulatory 3-month exercise training programmes are most often reimbursed, when clinical necessity is explained. Several rehabilitation clinics offer inpatient cancer rehabilitation. A study from the University Hospital of Zurich showed that 42% of cancer patients participated in inpatient rehabilitation programmes. Longer hospital stay, unemployment, supplementary health insurance and woman with advanced tumour stages were associated with programme uptake [17].

Cancer rehabilitation programmes may benefit from lessons learned in cardiac rehabilitation. Based on the EUROASPIRE IV and V surveys that have been conducted in 78 centres from 25 European countries, only half of all coronary artery disease patients were referred to and only 40% attended a cardiac rehabilitation program [18]. In heart failure patients, who have some similarities to cancer patients, such as exercise intolerance, referral and uptake are even lower [19]. This illustrates the unused potential for improving quality of life and outcomes for patients. Some barriers for implementation may be similar for cardiac and cancer patients. Healthcare professionals may doubt the value of exercise, and there may be a lack of available regional rehabilitation programmes and/or educated personnel. On a patient level, adherence to exercise may be low owing to socioeconomic factors, disease severity, co-morbidities, motivation, and personal beliefs and expectations [20]. Addressing these issues may contribute to a more holistic approach to cancer treatment, making exercise an important adjuvant therapy. There is an opportunity to use synergies between oncology and phase II / phase III cardiac rehabilitation. Cancer patients could be integrated in existing phase II cardiac rehabilitation programmes, based on their fitness level. Selected cancer patients may want to continue exercise during phase III in supervised programmes and may participate in one of the many regional heart groups in Switzerland (www.swiss-heartgroups.ch).

Safety of exercise in cancer patients

In general, exercise is safe and feasible throughout the cancer care pathway. Before beginning to exercise, a cancer-specific medical assessment is recommended. Exercise testing should be performed before moderate to vigorous exercises or sports. Relative and absolute contraindications may vary between cancer types and have to be respected (table 3) [21].

Table 3: Summary of the relative and absolute contraindications to some or all types of exercise and sport in cancer patients (modified from [13, 21]).

Relative contraindications	Recent weight gain (>2 kg during the 3 days preceding exercise)
	Decrease in systolic blood pressure during exercise
	New York Heart Association class IV cardiac status
	Ventricular arrhythmia at rest or during exercise
	Supine heart rate ≥100 beats/min
	Neurological toxicity >grade 2
	Asymptomatic central neurological lesions
	Asymptomatic bone metastases
Absolute contraindications	Progressive increase in dyspnoea at rest or during exercise for the 3–5 days preceding exercise
	Uncontrolled diabetes mellitus
	Acute disease or fever
	Recent embolism
	Thrombophlebitis
	Myocarditis or active pericarditis
	Symptomatic central neurological lesions
	Haematological toxicity: platelets <50 000/mm^3, leucocytes <1500/mm^3, haemoglobin <8 g/dl
	Symptomatic central neurological lesions
	Osteolytic or painful bone metastases

Gaps in evidence

Multiple research gaps remain in this field, including the need for greater specificity about the dose-response effects of specific modes of exercise training on specific endpoints and within a broader range of cancer populations, and data on participation of cancer patients in competitive sports [13].

Key points

- Cancer and cardiovascular diseases share modifiable risk factors.
- Adjuvant radio- and/or chemotherapies increase cardiovascular risk in cancer survivors.
- Exercise intolerance in cancer patients is multifactorial and contributes to their elevated cardiovascular risk.
- Exercise is safe and feasible throughout the cancer care pathway and positively affects physical function, body composition, quality of life and possibly prognosis in selected cancers. Cancer-specific contraindications have to be respected.
- Exercise training should be personalised and can be integrated into comprehensive cancer rehabilitation programmes.

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