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The benefits of exercise in cancer patients and the criteria for exercise prescription in cardio-oncology

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Abstract

Cancer and cardiovascular diseases are the leading causes of death in high-income countries. Cardiovascular complications can be found in cancer patients, being the result of so-called 'cardio-toxicity'. Therefore, it becomes essential to thoroughly investigate the origin of cardiac damage and the strategy to prevent it or to reverse the negative remodelling associated with cardiotoxicity. In this review the beneficial effects of physical exercise in cancer patients were analysed, particularly to prevent cardio-toxicity before its clinical manifestation. According to the relevance of exercise, we suggest strategies for exercise prescription with a tailored approach in these patients. In conclusion, physical exercise seems to be a promising and effective treatment for cancer patients during and after therapy and seems to counteract the negative effects induced by drugs on the cardiovascular system. Exercise prescription should be tailored according to patient's individual characteristics, to the drugs administered, to the personal history, and to his/her response to exercise, taking into account that different types of training can be prescribed according also to the patient's choice. A cardiological evaluation including exercise testing is essential for an appropriate prescription of exercise in these patients.

Keyword

Exercise, oncology, training, prevention, cardiotoxicity

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Cancer and cardiovascular disease: a common disease

Cancer and cardiovascular diseases are the leading causes of death in high-income countries. The Global Initiative for Cancer Registry Development estimated that there were 18.1 m new cancer cases and 9.6 m cancer deaths in 2018.[1] Cancer and cardiovascular disorders share common risk factors, including aging and unhealthy lifestyle such as smoking habit, alcohol abuse, unbalanced fat diet and physical inactivity. The overlap of risk factors leads to a common strategy of prevention, primarily focused on the management of lifestyle changes and the practice of regular exercise. Indeed, being physically active reduces the incidence of cancer by 48% and the mortality due to cancer by 27%.[2] Furthermore, cardiovascular complications found in cancer patients are the result of toxicity induced by drugs administered for cancer treatment, so-called 'cardio-toxicity'. In addition to pharmacological cardiac protection during cancer therapy, it becomes essential to thoroughly investigate the origin of cardiac damage and the strategy to prevent it or to reverse the negative remodelling associated with cardiotoxicity. Exercise is able to reduce some negative effects due to chemotherapy such as fatigue, pulmonary and immune system dysfunction, lymphoedema and toxicity for the heart.[3]

In this review we report the beneficial effects of physical exercise (PE) in cancer patients to prevent cardio-toxicity

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before its clinical appearance. According to the relevance of exercise, we suggest a proposal for exercise prescription in this population based on a tailored approach.

Pathophysiological mechanisms of the beneficial effects of exercise in oncology

Several pathophysiological mechanisms can explain the beneficial effects of PE for the prevention of side effects in cancer patients. These mechanisms responsible for the benefits of exercise are summarised in Figure 1. According to these mechanisms, PE protects against ischaemia, toxic drug reactions[4] and limits the growth of the tumour.[5,6]

Exercising after the diagnosis of cancer: the beneficial effects of exercise in secondary prevention

Cancer patients are often more physically inactive than adults without cancer and from 53–70% of cancer survivors do not follow the recommended physical activity guidelines.[7] However, exercising is crucial for cancer patients undergoing oncological therapies. A meta-analysis carried out on 50,000 patients with colon and breast cancer reveals that exercising for 150 min per week is associated with a reduction of 24% and 28% of total mortality risk for breast and colon cancer survivors, respectively, compared with sedentary patients.[8] Furthermore, an inverse relationship between functional capacity and perioperative complications has been demonstrated by West et al.:[9] the authors performed preoperative cardiopulmonary exercise tests in patients undergoing colorectal surgery and at multivariate analysis they found that a threshold of peak oxygen uptake (V_{O2}) of 11.1 ml/kg/min or less was associated with a greater likelihood of postoperative complications (odds ratio (OR): 7.56). The mortality rate was found to decrease as peak V_{O2} increased. Therefore, current data emphasise the importance of PE in patients diagnosed with cancer who are under treatment, irrespective of the type of treatment itself.

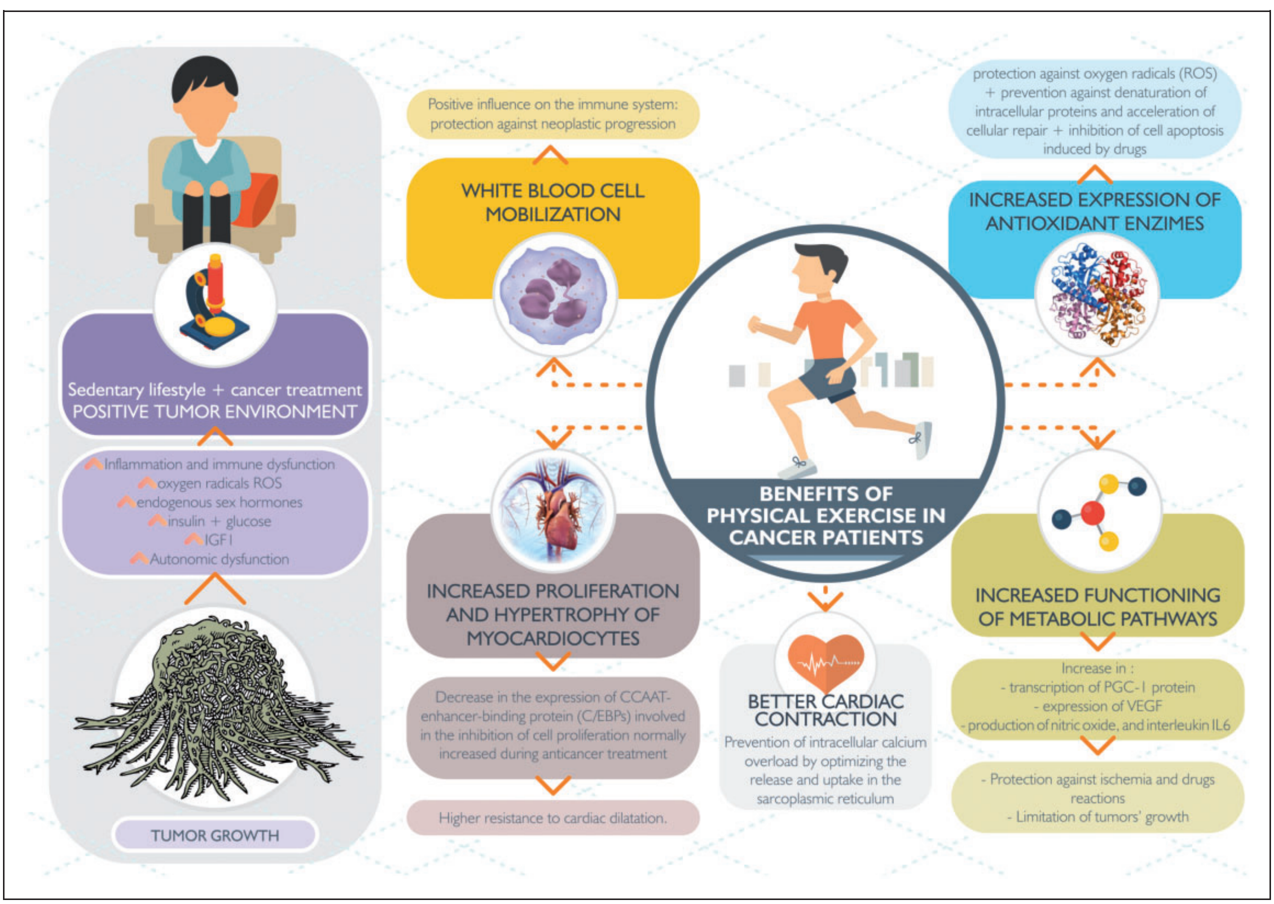

Figure 1. Pathophysiological mechanisms responsible for the benefits of exercise. Comparison between active vs sedentary lifestyle in cancer patients. CCAAT-enhancer-binding proteins: cytosine-cytosine-adenosine-adenosine-thymidine enhancer-binding proteins; IGF1: insulin-like growth factor; PGC1: peroxisome proliferator-activated receptor γ coactivator 1; ROS: reactive oxygen species; VEGF: vascular endothelial growth factor.

The beneficial effects of PE have been documented both for supervised sessions and for unsupervised sessions conducted at home.[10] Among the cancer survivors participating in individualised home-based aerobic and resistance exercises for 12 months, a significant improvement in lower body muscle strength was observed as well as a decrease in waist circumference, body cell mass and extracellular mass.[11] Wenzel et al. studied 138 patients with different types of cancer (prostate, breast and other solid cancer) randomised to home-based walking intervention or usual care.[12] The exercise group ($n = 68$) reported more vigour ($p = 0.03$) and 11% less fatigue ($p < 0.001$) than control group participants ($n = 58$).[12] Similarly, Griffith et al. demonstrated that participants who were engaged in a home-based walking programme were found to have better self-reported physical function ($p = 0.037$) and less pain ($p = 0.046$) than those in the usual care group.[13] Therefore, for patients unable to undergo intense supervised exercise, home-based low-intensity PE represents a possible alternative. Although Van Waart et al. have proven that two supervised sessions consisting of a 30-minute aerobic workout plus a 20-minute resistance training are more effective than three 30-minute aerobic workouts at home, the authors concluded that both types of training are effective for a faster return to work as well as less nausea, vomiting and pain after chemotherapy, as compared with a sedentary approach.[14] In cancer patients, exercise has also been shown to counterbalance the side effects of radiotherapy. A meta-analysis that included nine studies and 802 patients clearly established that PE can reduce fatigue and improve quality of life after radiotherapy.[15] Furthermore, the 'Hormones and Physical Exercise' study demonstrates that PE can induce positive outcomes on the bone mineral density and on the immune system in 121 women treated with aromatase inhibitors.[16] Two sessions per week of moderate-high intensity aerobic and resistance exercise reduced the severity of adverse changes in body composition, physical function, total cholesterol/high-density lipoprotein (HDL)-cholesterol ratio, sexual function, fatigue and psychological distress, while improving social functioning and mental health in men with prostate cancer.[17]

The utility of exercise is crucial even when medical therapy fails such as in triple negative breast cancer (TNBC). TNBC has an aggressive behaviour, lack of targets for targeted therapies and shows an early peak of relapses. The beneficial responses of TNBC survivors to regular exercise, including a reduction in the rate of tumour growth, are becoming increasingly evident. New evidence of the effects of exercise on TNBC prevention, control and outcomes is based on the inhibition of phosphatidylinositol-3-kinase, protein kinase B and the mammalian target of rapamycin. Women with TNBC who practice regular PE in the first six months after the diagnosis of cancer have a lower risk of total mortality and disease-specific relapses mortality, with hazard ratio (HR) adjusted by 0.58 and 0.54, respectively, as compared with women who are inactive.[18] Exercise can also significantly lead to a delay of tumour growth in association with chemotherapy. Jones et al. demonstrated in patients under treatment with doxorubicin-cyclophosphamide and practising three sessions of exercise per week that, in addition to an increase in maximum oxygen consumption, a magnification of endothelial function is also observed as an increase in tumour perfusion.[19] Although it may seem contradictory, this greater perfusion brings a greater effect of the chemotherapeutic drug which better reaches neoplastic cells, delaying tumour growth.[19]

Cancer survivors: effects of exercise to prevent relapses and cardiovascular disease

Breast cancer survivors live for many years and may develop chronic conditions.[20] Moreover, they have an increased risk of relapses, second cancers, cardiovascular disease, bone loss, weight gain, arthralgias, cognitive dysfunction, fatigue and psychosocial distress.[21] Epidemiological evidence consistently shows a relationship between PE and survival post-breast cancer. In an Australian population of 337 breast cancer women after a median follow-up of 101 months, there were 15 out of 130 (11.5%) survival events in the usual care group, compared with 11 out of 207 (5.3%) events in the exercise group.[22] Disease-free events for the usual care vs exercise group were 23/130 (17.7%) and 25/207 (12.1%), respectively. The corresponding unadjusted HR for the exercise group for overall survival was 0.45 (95% confidence interval (CI), 0.21–0.97; $p = 0.037$) and for disease-free survival was 0.66 (95% CI, 0.38–1.17; $p = 0.155$).[22]

In a meta-analysis including 22 studies with breast cancer survivors, a protective effect of PE on death and all causes related to cancer has been documented: physical activity both before and after the diagnosis was associated with fewer events related to cancer such as relapses (HR = 0.79) and tumour progression (HR = 0.72).[23] The beneficial effects of exercise in the prevention of disease relapses can be observed even in a short-term follow up. Brown et al.[24] studied changes in soluble intercellular adhesion molecule-1 (sICAM-1) as a prognostic biomarker in survivors of stage I–III colon cancer, according to its implication in promoting the growth of existing micro-metastases and the formation of new micro-metastases.[25] Patients were randomised to usual care control, 150 min/week of aerobic exercise (low-dose) or 300 min/week of aerobic exercise (high-dose). Both doses of exercise elicited physiologically significant effects on sICAM-1.[24] Exercise reduced sICAM-1 with a dose-response effect: indeed, compared with the control group, over six months sICAM-1 decreased by –134.9 ng/ml (95% CI, −238.1 to −31.6) in the low-dose group and −114.8 ng/ml (95% CI, −222.5 to −7.1) in the high-dose group.[25] Furthermore, in patients with stage III colon cancer treated with surgery plus chemotherapy, it has been shown that those who practiced at least 18 metabolic equivalent of task (MET)-h per week (i.e. the equivalent of walking six or more hours per week at an average pace) of PE had a significant improvement of 47% in the occurrence of relapses compared with inactive patients (p for trend = 0.05).[26] Richman et al. demonstrated a significant inverse association between the risk of prostate cancer progression and brisk walking after diagnosis of localised prostate cancer: patients who walked briskly for ≥3h/week had a 57% lower rate of progression compared with men who walked at an easy pace for <3 h/week (HR = 0.43; 95% CI, 0.21–0.91; p value = 0.03).[27]

The incidence of treatment-induced progressive decline in left ventricular (LV) function to overt heart failure is a major but still under-recognised cause of mortality in long-term cancer survivors.[3] Long-term cardiotoxicity appears to be particularly relevant in children, since almost 80% of them live more than 15 years after cancer diagnosis and cardiotoxic complications were described up to 30 years after treatment in 8.3% of survivors.[28,29] Cardiovascular disease is the second leading cause of long-term morbidity and mortality among child cancer survivors and it is already the most common cause of death for women.[30,31] The Framingham risk score (FRS) is a reliable method for predicting the 10-year risk of developing cardiovascular disease which can also be used in cancer patients.[32,33] Higher FRS is reported in overweight patients with early-stage breast cancer. Lee et al. examined the effects of a 16-week aerobic and resistance exercise intervention based on three sessions per week on the FRS in 100 women with stage I–III breast cancer in a prospective randomised clinical trial.[34] The FRS was calculated for each participant using preset points for each of the six FRS categories: age, systolic blood pressure, HDL cholesterol, low-density lipoprotein cholesterol, diabetes presence and smoking status. Patients were randomised to exercise ($n = 50$) or usual care ($n = 50$). The post-intervention FRS was significantly reduced in the exercise group compared with the usual care group (mean, −9.5; 95% CI, −13.0 to −6.0), which corresponds to a 11% (95% CI, −15.0 to −5.0) decrease on the FRS-predicted 10-year risk of developing cardiovascular disease.[34]

Jones et al. investigated the association between PE and cardiovascular disease in two population-based cohort studies of women ($n = 2,973$) diagnosed with non-metastatic breast cancer, in the Life After Cancer Epidemiology and Pathways study.[35] There was a 9% (HR = 0.91; 95% CI, 0.76–1.09), 21% (HR = 0.79; 95% CI, 0.66–0.96), and 35% (HR = 0.65; 95% CI, 0.53–0.80) reduction in the risk of cardiovascular events for women engaged in 2–10.9 MET-h/week, 11–24.5 MET-h/week, and ≥24.5 MET-h/week, respectively. The same results were obtained by Palomo et al. in 4015 participants with non-metastatic breast cancer.[36] After a long-term follow-up, a decreased risk for cardiovascular events (HR = 0.59) and coronary heart disease death (HR = 0.41) was observed in the cases of higher levels of exercise. Testicular cancer survivors have an increased risk of treatment-related cardiovascular disease, which may limit the overall survival.[37] High-intensity aerobic interval training were shown to elicit improvements among traditional and cardiovascular risk factors in these patients.[38] The main effect observed is an improvement in peak aerobic fitness V_{O2} which is the most significant surrogate markers of human health, longevity and cardiovascular risk.[39,40] Recent observational evidence in testicular cancer survivors treated with cisplatin suggests that PE is protective against adverse health outcomes.[41] Each 3.5 ml O_2/kg/min improvement in V_{O2} peak was associated with a 10–25% relative risk reduction in overall mortality.[42] Courneya et al. randomised 301 breast cancer patients to three exercise regimens: standard (25–30 min of aerobic exercise), high (5–60 min of aerobic exercise) and combined high plus resistance exercise.[43] All groups presented a decline in peak V_{O2} from baseline to completion of chemotherapy. However, this decline was partially attenuated in the high exercise group (ΔV_{O2}peak −2.5 ml/kg/min) vs standard or combined groups (ΔV_{O2}peak −3.4 ml/kg/min and −3.6 ml/kg/min, respectively).[43]

Effects of exercise on the prevention and treatment of cardiotoxicity

Cardiotoxicity prevention refers to the role that exercise has in preventing myocardial damage caused by drugs. Chicco et al. demonstrated in 2006 for the first time that chronic PE before doxorubicin treatment protects against decrease in LV systolic function in trained rats.[44] Although robust evidence is still lacking, a protective effect of exercise is supposed to be found also in patients. Preparing the body to tolerate a stressful event such as chemotherapy was termed 'prehabilitation'. De Paleville et al. published a case study of a 42-year-old woman, a newly diagnosed breast cancer patient, which highlighted the efficacy of introducing aerobic training one week prior and continuing exercising over a eight-week period of chemotherapy in terms of reduction of fatigue and improvement in functional ability.[45] In 2018, Kirkham et al. emphasised that breast cancer patients have modest and variable adherence to exercise during chemotherapy, because of symptoms related to drug treatment.[46,47] Therefore, they planned a study evaluating the effects of 30 min of vigorous-intensity treadmill walking performed 24 h prior to every anthracycline treatment.[5,6] A 100% adherence to physical activity and no adverse events were demonstrated. Furthermore, exercise sessions significantly attenuated N-terminal pro b-type natriuretic peptide (NT-proBNP) at 24–48 h after the first treatment.

This preliminary evidence suggests that exercise as a treatment should be started as soon as possible and seems to be useful in patients before initiating chemotherapy. Chemotherapy and antiangiogenic drugs are related to an increased risk of cardiac damage, such as LV dysfunction and heart failure due to anthracyclines, hypertension due to bevacizumab, vasospastic and thromboembolic ischaemia due to antimetabolites, hormonal therapy and arrhythmias due to taxanes.[48] There is a strong relationship between cardiorespiratory fitness and the risk of cardiovascular events and mortality.[49,50] Howden et al. confirmed the value of exercise in breast cancer patients. In the usual care group, they observed a 15% reduction in peak V_{O2} during a four-month period of anthracycline-based chemotherapy and the extent of the decrease was significantly less for the exercise group than the usual care group.[51] This reduction approximates the change that would be expected with 15 years of aging.[52] Hughes et al. published case studies for two cancer survivors: a 56-year old female Hodgkin's lymphoma survivor (Pt #1) and a 44-year old male leukaemia survivor (Pt #2).[53] After a 16-week exercise programme (30 min of exercise performed three times/week at a minimum intensity of 50% of heart rate reserve) both patients improved in V_{O2} peak while ejection fraction (EF) increased only for Pt #2 but not for Pt #1.[53] Nagy et al. reported the effect of regular PE on diastolic function and on the symptoms of late heart failure in case of anthracycline chemotherapy.[54] This prospective study included 55 female patients with breast cancer and no cardiovascular risk factors. Five years after the treatment, symptoms of heart failure were less frequently reported in the PE group than in the inactive one (19.45% vs 68.42%, $p = 0.0017$). Notably, LV diastolic dysfunction related to anthracycline therapy became evident in the PE group later and symptoms of heart failure were less frequent than in the non-active group.[54] Järvelä et al. studied 21 long-term survivors of childhood acute lymphoblastic leukaemia with preserved LV systolic function and decreased diastolic function.[55] The attenuated LV diastolic function improved significantly after a home-based exercise programme. Early diastolic mitral inflow velocity E and e' increased ($p = 0.04$ and $p < 0.01$, respectively). Peak circumferential systolic and diastolic strain rates at midlevel improved after the exercise programme ($p = 0.04$ and $p < 0.01$, respectively).[55]

Conversely, Haykowsky et al. found that cancer patients treated with trastuzumab, known to cause a decrease of left ventricular ejection fraction (LVEF) and heart failure, experienced a dilatation of the left ventricle and a decrease of LVEF (pre: $64 \pm 4\%$ vs post: $59 \pm 4\%$, $p < 0.05$) despite aerobic training (a supervised aerobic training three days per week during the initial four months of trastuzumab therapy).[56] These findings could be at least explained by the incomplete adherence of patients to high-intensity aerobic exercise needed to attenuate LV dysfunction mediated by trastuzumab.[56] Although few data are available on the potential positive effects of exercise on cardiotoxicity, the preliminary results seem to be promising and further studies are needed to identify the best type of exercise and to understand whether in some types of anticancer therapy the responses to the beneficial effects of PE is attenuated.

Exercise prescription in cardio-oncology: a tailored approach

Rehabilitative pathways for cancer patients are aimed at implementing cardiorespiratory fitness and systemic functions with consequent benefits in terms of symptoms, quality of life, mortality and relapses of cancer (Figure 2).

A multidisciplinary approach based on physical training and therapeutic optimization, lifestyle advice, control of risk factors and psychological support is strongly recommended in all cancer patients. Furthermore, the American Cancer Society and the American Heart Association have introduced the concept of cardio-oncology rehabilitation, 'CORE', which includes identification of patients with cancer at high risk for cardiac dysfunction. The CORE programme is based on a multimodality approach that includes exercise plus nutritional counselling and cardiovascular risk factor assessment to prevent or moderate cardiovascular events.[57]

Deconditioning, fatigue, cachexia and mobility impairment may require targeted interventions. Understanding the natural history of cancer, its risk and treatment response to tailored treatment strategies is becoming the paradigm in clinical intervention[58] also because heterogeneous responses to the same physical training protocol have been demonstrated for the improvement of cardio-respiratory fitness.[59] In order to tailor the workload in the gym for cancer patients, lactate testing and cardiopulmonary exercise testing

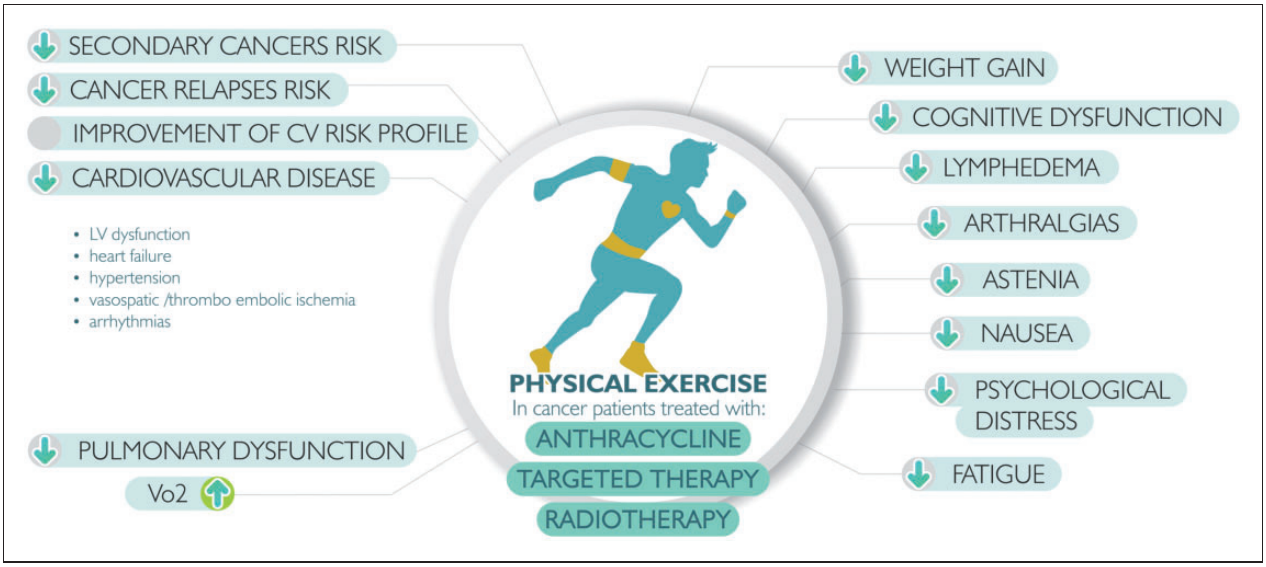

Figure 2. Beneficial effects of physical exercise in cancer patients undergoing oncological treatment. LV: left ventricular; Vo2: peak oxygen uptake.

may help in understanding the individual response of a patient to exercise,[60] identifying his/her response to exercise and the aerobic and anaerobic thresholds, useful for a tailored exercise prescription based on the use of these thresholds and the corresponding HRs for calibrating the intensity of the PE. For an individualised exercise prescription it is also important to take into account the so-called 'cancer-induced cardiac cachexia', a multi-organ and/or multi-tissue syndrome affecting brain, liver and heart characterised by inflammation and weight loss of at least 5% due to a strong wasting of muscle mass and fat tissue, that can be also present in therapy-naive patients due to the tumour environment. It has been demonstrated that PE can counteract cachexia by restoring both muscle strength and endurance[61] and may be an adjuvant and therapy for cancer-related disorders.[62]

The main goals for physical activity in cancer patients are: (a) maintain good physical and social function; (b) optimise the ability to provide an individually adapted treatment; (c) reduce symptoms, with respect to nausea and fatigue in particular; (d) attain an optimal weight and avoid unfavourable weight gain or weight loss.

Potential contraindications

Although the current evidence is not enough strong to allow a clear definition of potential contraindications to exercise training in cancer survivors, we summarised the recommendations, suggestions and practical approaches currently available. Although the presence of ongoing treatment could be regarded as a relevant limitation to exercise programmes in cancer patients, it does not represent *per se* an absolute contraindication. However, exercise training modalities should be discussed with the responsible physician, in cooperation with the physiotherapist, and adjusted as necessary. As suggested by the Swedish Professional Associations for Physical Activity in a textbook edited in cooperation with the Swedish National Institute of Public Health, it is important to remember that the cancer disease, ongoing treatment and blood profile, for example, low haemoglobin levels, affect the type of activity that should and can be performed.[63] Therefore, during ongoing treatment, the following special precautionary measures should be taken: (a) always consult the physician responsible for treatment before beginning an activity; (b) avoid activities that: – require high intensity in patients with low haemoglobin levels, <8.0 g/dl; – entail an increased risk for bacterial infection in patients with a low white blood cell count, $<0.5 \times 109$/l; – can lead to an increased risk of bleeding in cases where thrombocyte levels are $<50 \times 109$, such as contact sports; (c) in the case of exercise-related symptoms, investigate the cause, particularly for dyspnoea. In the case of leg pain, avoid activities that can lead to increased risk of fracture while, in the case of pronounced fatigue, plan daily activities of a low to moderate level, balanced with rest. The presence of fatigue should be investigated: indeed, according to the National Comprehensive Cancer Network (NCCN) guidelines, exercise should be used with caution in survivors with limitations due to metastases or fatigue as well as in those with bony metastases, thrombocytopenia, anaemia, fever, active infection.[64]

However, starting an exercise programme is a recommended treatment (category 1 level evidence-high level evidence and uniform NCCN consensus) also for fatigue.

Mina et al.[65] developed a 'Safety Reference Guide' to identify and manage many potential exercise contraindications. Among the relative contraindications to exercise we find: haemoglobin concentrations <80 g/l; white blood cell concentrations $<2.0 \times 109$/l; neutrophils concentrations $<1.5 \times 109$/l (neutropenia) or fever (oral temperature >38°C/100.4°F); systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg after two measurements; resting heart rate >120 bpm after two measurements, five minutes apart; adverse cardiorespiratory signs or symptoms: increasing chest pain, fatigue, shortness of breath, wheezing, claudication. The presence of moderately-to-severe angina, dizziness or pre-syncope, cyanosis or pallor and resting oxygen saturation on room air <88% represent absolute contraindications to exercise.

The current guidelines recommend people to be as physically active as possible during cancer treatment and supports the start of exercise referral at the time of diagnosis and treatment, being PE safe for people with cancer both during active treatment and after treatment.[66,67] However, a tailored approach based on clinical re-evaluation according to the presence of symptoms or potential ongoing relevant cardiotoxicity with a further adaptation of training programmes is strongly suggested.

Despite these recommendations, the current data available in the literature have demonstrated the effectiveness of starting exercise programmes during the pharmacological treatment compared with postponing this intervention. However, there are no studies that focus their attention on the most appropriate timing between the administration of intravenous anthracycline and the starting of an exercise programme. For patients undergoing radiotherapy, water-based exercise training should be avoided. Notably, exercising immediately after a radiotherapy session may lead to the appearance of electrocardiographic changes demonstrated during the exercise testing, which means that the heart is undergoing cellular suffering, with a cellular damage related to radiotherapy being localised to the irradiated area;[68] therefore the most appropriate timing to begin physical exercise must be personalised to the patient and to the type of tumour present.

Type of prescription

General and specific recommendations for physical activity in adults including cancer are summarised in Table 1.[69] Both endurance and resistance training are known to stimulate cardiac muscle trophism, but endurance training is considered more effective to improve cardiovascular performance and to exert anti-inflammatory properties. However, endurance training can be sometimes difficult to sustain for cancer patients and particularly for frailty and debilitated patients. Resistance training, according also to its greater anabolic potential, may be more appropriate as starting point for an exercise-therapy programme in cancer patients.[70]

Resistance training

The optimal resistance training programme for cancer survivors and its dose-response relationship have not yet been defined. Resistance training is defined by:

1. Loading - intensity, which describes the amount of weight to be lifted (usually expressed as a percentage of repetition maximum (RM)).
2. Volume, which depends on the number of sets and repetitions for each session (inversely related to the loading).
3. The frequency of resistance training sessions, usually expressed as the number of sessions per week.

In a recent meta-analysis, Strasser et al. reported that total body training could increase muscle strength and improve lean body mass.[70] Furthermore, the application of resistance training in the upper body improves pain and disability especially in patients treated for breast and head cancer. The effects seem to be beneficial especially in patients with breast, prostate, head and neck cancer, improving muscle function and body composition without any special adverse effects. International guidelines[69,71] provide information to establish the basic principles for adequate programmes but specific recommendations for intensity and volume of resistance training are lacking.

The series of repetitions should be continued until it is difficult to continue exercising. If the goal is to improve muscle strength and trophism, a series of 8–12 repetitions performed at slow-moderate velocity is considered effective. Since the development of force is progressive, a gradual increase in the weight and in the number of set (up to 3–4) is necessary to stimulate further improvements. It has been reported that there is a significant negative impact on upper limb muscle strength with increasing intensity: low/moderate-intensity RT (lower 75% of 1 RM) was associated with greater improvement than moderate/high intensity RT (over 75% of 1 RM).[70] These findings suggest that the stimulus for protein synthesis may depend more on load volume rather than intensity. This could be important for cancer patients for whom a high intensity (i.e. the weight to be lifted) might be

Table 1. Key recommendations for exercise prescription in cancer patients.

General principles

The time must be adapted to the individual's situation, age and previous experience of physical activity and exercise.

When patients are not able to meet the following key guidelines, they should engage in regular physical exercise according to their abilities and should avoid inactivity.

Cancer patients can have absolute or relative contraindications to exercise: see text for details.

Exercise dose is determined by: (a) frequency; (b) duration; (c) intensity.

Frequency and duration

- From 150–300 min per week of moderate intensity.
- Or from 75–150 min per week of vigorous intensity aerobic physical activity.
- Or an equivalent combination of both.
- Muscle-strengthening activities of moderate or greater intensity and that involve all major muscle groups on 2 or more days per week.
- Flexibility training should be performed at least 2–3 times per week, such as stretching (10–20 s), four times per muscle group.
- Respiratory muscle training should be performed three times per week, with a duration of 30–60 min.

Intensity

- Moderate endurance training: Borg Scale 12–14; 50–70% peak V_{o2}; BL 2–4 mmol/l[a]; 60–80% maximum heart rate.
- Vigorous endurance training: Borg Scale >14; 60–80% peak V_{o2}; BL 3–5 mmol/l[a]; 70–90% maximum heart rate.
- Resistance training: intensity should correspond to 50–70% of 1 RM.
- Respiratory muscle training: 30% of maximum inspiratory pressure.

According to the literature currently available, moderate exercise should correspond to an intensity slightly above the 1st ventilatory threshold or LT while vigorous exercise should correspond to an intensity slightly below the 2nd ventilatory threshold. The corresponding percentages of maximum heart rate and peak V_{o2} can be individually determined. As a consequence, the range of intensity of training can significantly change according to training and clinical status.

Progression

Frequency: start with a weekly session and introduce the second session when the patient is adapted (2–3 times per week is considered the optimal frequency).

Duration: start with 10–30 min of endurance training and increase of 10 min every week to reach the optimal weekly training volume in 3–4 weeks.

Intensity: During the first 3–4 weeks, starting with a lower intensity, then progress with the suggested intensity. The progression should take into account patient's adaptation to exercise, previous experience of training, age and clinical conditions.

The patient should start gradually with 1–3 sets of 8–10 resistance exercise, increasing weekly training volume according to his/her adaptation.

Specific principles

Select the appropriate exercise from multiple-joint basic exercises for major large muscle (chest press, shoulder press, squat, abdominal crunch. . .).

Introduce progressively single-joint basic exercise in each session after multiple-joint exercises (biceps curl, triceps extension, leg extension. . .).

Rotation of exercises (upper and lower body and opposing agonist-antagonist).

To have more effect in counteracting protein catabolism: start training volume from one set to increase progressively to three sets (or more) of 8–12 repetitions. In this manner the last repetition is made with a perceived effort that discourages the next repetition.

Interval of rest between sets should be 1–2 min.

Velocity of execution should be slow-moderate. Duration of concentric phase of about 2 s; duration of eccentric phase: 2–4 s; duration of the set is at least 40 s.

Avoid Valsalva manoeuver during weight lifting.

BL: blood lactate; LT: lactate threshold; RM: repetition maximum.

One RM corresponds to the maximum weight that can be lifted through the entire exercise movement only one time. Maximum heart rate and peak V_{O2} are intended as the maximal values individually determined by stress testing. [a]Lactate level during moderate exercise is constant at 2–4 mmol/l while during vigorous exercise is constant or slightly increasing, usually between 3–5 mmol/l.

more difficult to sustain than a high volume (i.e. the number of repetitions). Key recommendations for the prescription and progression of resistance training adapted to cancer survivors are summarised in Table 1.[69,71,72]

Aerobic training

In aerobic training, most of the body muscles usually move in a cyclic manner to allow human locomotion with the necessary energy provided by the aerobic mechanism (i.e. walking, running, bicycling, swimming, cross-country skiing).

Aerobic activity is defined by three components that determine the characteristics of aerobic training: (a) intensity, which depends on the energy metabolism rate and which is often indicated as light, moderate or vigorous; (b) frequency of aerobic activity sessions usually expressed in the number of weekly sessions and (c) duration of the activity for each session.

According to international guidelines, the duration (minutes of moderate or vigorous per week) may be more important than the other components.[69,71] However, the definition of the intensity of exercise (e.g. moderate vs vigorous) is crucial for exercise prescription. In order to define exercise intensity, the so-called 'Talk test' may represent an interesting reference.[73] While a patient who practices moderate-intensity aerobic activity may be able to talk during exercise (but not to sing), a patient who performs vigorous activity is able to say only few consecutive words before a pause for breath. Another way to quantify the intensity of exercise is the rate of perceived exertion (RPE) according to the original Borg Scale or category scale (6–20 scale) and the revised category-ratio scale (CR10; 0–10 scale). In the CR10 scale, a moderate intensity corresponds to an RPE value of 3–4, while vigorous intensity corresponds to an RPE of 5–6. In the original Borg Scale a moderate activity registers 11–14 ('fairly light' to 'somewhat hard'), while vigorous activity usually rates a 15 or higher ('hard' to 'very, very hard').[74] The use of cardiopulmonary exercise testing and incremental testing is a useful method to define training intensity for each specific patient, according to his/her characteristics and the response to exercise. Particularly for lactate testing, the determination of blood lactate for each step and the subsequent analysis of the lactate-intensity curve, is considered an accurate and reliable method to customise the intensity of aerobic exercise, even in patients with particularly reduced aerobic fitness.[75] According to the lactate-intensity relationship, the intensity between 2–4 mmol/l of blood lactate (indicative of the first lactate threshold or aerobic threshold) is to be considered light-to-moderate while vigorous intensity corresponds to an amount greater than 4 mmol/l (indicative of the second lactate threshold or anaerobic threshold).[76] Regarding the relationship between aerobic training volume and beneficial effects on the heart, it has been estimated that physical activity of over 1,500 cal per week was related to about 40% overall reduction in cardiovascular risk in comparison with those activities of less than 200 cal per week.[77]

The energy cost of walking on flat terrain is about 2 kcal per kg of body mass per km covered (at the most economical speed of 4 km/h).[78] This means that to consume 1,500 kcal per week, a person of 75 kg of body mass must walk at least 20 km per week. Considering 4 km/h of average speed, this means five hours (300 min) per week of walking. This weekly training volume corresponds to what is indicated (as a higher value) by the already mentioned international guidelines.[69,71]

In healthy subjects this intensity allows walking at an intensity below the ventilatory threshold (according to the talk test) which, therefore, can be classified as moderate. However, the same intensity, could be vigorous (or even unsustainable because excessively intense) for a cancer patient presenting cachexia and other treatment-correlated symptoms.

High-intensity interval training has become popular in the last years as an alternative to continuous aerobic training and its safety and beneficial effects have been demonstrated in several settings, such as coronary artery disease, heart failure and metabolic syndrome. Unfortunately, few data are currently available in literature about its effects in cancer patients. Dolan et al. studied postmenopausal breast cancer survivors, during six weeks, who were randomised into three groups: supervised aerobic interval training, supervised continuous moderate exercise training, and an unsupervised control group. Compared with the control group, cardiorespiratory fitness improved in aerobic interval training and continuous moderate exercise training by 12% ($p < 0.001$) with no significant difference between exercise groups. Aerobic interval training had a greater influence on lower extremity strength ($p = 0.026$) and body weight ($p = 0.031$).[79] Toohey et al. studied, in 16 cancer survivors, the effects of low-volume high-intensity interval training ($n = 8$) and continuous low to moderate intensity training ($n = 8$) on functional capacity, quality of life and cardiovascular disease risk factors. After 36 sessions (12 weeks) of supervised exercise, significant positive effects were observed in the six-minute walk test both in the continuous and in the interval training group. Both exercise strategies induced an improvement in quality of life, functional capacity and selected cardiovascular disease risk factors; furthermore, the interval training programme was well tolerated and was the preferred modality to improve fitness.[80] Therefore, although only preliminary data are available, interval training could be an alternative modality to be applied in cancer patients who could obtain similar beneficial effects as compared with traditional continuous training programmes.

Inspiratory muscle training (IMT)

IMT can decrease dyspnoea, by strengthening the inspiratory muscles and by offering means for controlled breathing and can also facilitate the increase in the level of activity and improve the quality of life, particularly in thoracic cancer patients. IMT is feasible and potentially effective in cancer patients and is associated with significant improvement in peak V_{O2}, maximal inspiratory and expiratory pressures, with important clinical effects on distress from breathlessness, ability to cope with breathlessness, satisfaction with breathlessness management, fatigue as well as depression and emotional function.[81,82] IMT is effective for functional capacity and parameters of medical care if performed for 1–4 weeks, performing 1–3 sessions a week, with moderate intensity (50% for endurance capacity).[82] Therefore, IMT seems to be useful and effective, particularly in thoracic cancer patients and could be prescribed in this specific population.

Conclusions

PE seems to be a promising and effective treatment for cancer patients during and after therapy and seems to counteract the negative effects induced by drugs on the cardiovascular system, the so-called 'cardio-toxicity'. Exercise prescription should be tailored according to patient's individual characteristics, to the drugs administered, to the personal history, and to his/her response to exercise, taking into account that different types of training that can be prescribed according also to the patient's choice. Future studies are needed to establish the safety and tolerability of exercise in cancer patients with a particular attention in understanding the most appropriate and most beneficial training programme.

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Author contribution

FDA, FA, CF, RM, MB and SM contributed to the conception or design of the work. FDA, FA and CF drafted the manuscript. FDA, FA and CF contributed to the acquisition, analysis, or interpretation of data for the work. All the authors critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy

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