Published in final edited form as:
Nat Rev Clin Oncol. ; 9(5): 288–296. doi:10.1038/nrclinonc.2012.27.

Exercise rehabilitation in patients with cancer

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Abstract

Emerging evidence indicates that patients with cancer have considerable impairments in cardiorespiratory fitness, which is likely to be a result of the direct toxic effects of anticancer therapy as well as the indirect consequences secondary to therapy (for example, deconditioning). This reduced cardiorespiratory fitness is associated with heightened symptoms, functional dependence, and possibly with an increased risk of cardiovascular morbidity and mortality. Current understanding of the complex interaction between the effects of the tumour and cancer-associated therapies on the organ components that govern cardiorespiratory fitness, and the effects of exercise training on these parameters is limited; further research will be critical for further progress of exercise-based rehabilitation in the oncology setting. We assess the current evidence regarding the level, mechanisms, and clinical importance of diminished cardiorespiratory fitness in patients with cancer. The efficacy and adaptations to exercise training to prevent and/or mitigate dysfunction in conjunction with exercise prescription considerations for clinical use are also discussed.

Introduction

Structured exercise training is established as the cornerstone of primary and secondary disease prevention in multiple clinical settings.[1] In stark contrast, the role of exercise following a diagnosis of cancer has, until recently, received comparably less attention.[2] The precise reasons for this are unknown but likely stem from the prevailing dogma that a cancer diagnosis is associated with poor prognosis, immune deficiency, and other severe debilitating side effects that preclude participation in, and benefit from, exercise training. Modern cancer management typically involves aggressive and prolonged combination

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Competing interests
The authors declare no competing interests.

Author contributions
S. G. Lakoski and L. W. Jones researched data for the article. N. D. Eves, P. S. Douglas and L. W. Jones made a substantial contribution to the discussion of the content, S. G. Lakoski, N. D. Eves and L. W. Jones wrote the article and all authors edited and revised the manuscript prior to submission.

locoregional and/or systemic therapy that causes a plethora of acute and long-term toxic effects leading to considerable functional morbidity and an increased risk of mortality from non-cancer-related causes.[2] Exercise training is a pleiotropic therapeutic strategy with the capacity to act across multiple organ systems[3] to facilitate attenuation and/or prevention of cancer therapy-associated morbidity as well as improve clinical outcomes in patients with cancer.[4] The purpose of this article is to review the current evidence regarding the level, mechanisms, and clinical importance of diminished cardiorespiratory fitness in patients with cancer. In addition, we also discuss the efficacy and mechanisms of exercise training to prevent and/or mitigate the adverse effects of therapy as well as provide exercise prescription guidelines for clinical practice.

Cardiorespiratory fitness

Definition of cardiorespiratory fitness

Cardiorespiratory fitness is determined by the transport and use of oxygen from the environment to the skeletal muscle mitochondria; therefore, it is governed by the integrative capacity of several organ components including the pulmonary and cardiovascular systems, the vasculature, blood, and skeletal muscle.[5] Oxygen transport and use occurs via a series of convective and diffusive steps involving a sequential reduction in the partial pressure of oxygen, commonly termed the oxygen cascade.[6] In this article, we use the oxygen cascade as a central framework to explain the factors contributing to reduced cardiorespiratory fitness and efficacy of exercise training to augment cardiorespiratory fitness.

Cardiorespiratory fitness measurement

In current oncology practice and clinical trials, the physiological status of patients is typically assessed through subjective performance status scoring systems (for example, Karnofsky Performance Status [KPS]) or evaluation of individual cardiac and/or pulmonary function at rest via echocardiography or spirometry, respectively. By contrast, an evaluation of cardiorespiratory fitness provides an assessment of the integrative capacity of the cardiovascular, haematopoietic, and musculoskeletal systems during stress (that is, aerobic exercise).[7] There are several methods available that provide an objective determination of cardiorespiratory fitness (Table 1), and international guidelines on the proper conduct of cardiorespiratory fitness testing are available.[7–10] An incremental cardiopulmonary exercise test with gas exchange measurement, to assess peak oxygen consumption (VO_{2peak}), provides the gold standard assessment of cardiorespiratory fitness.

Evidence of impaired fitness

Persuasive evidence is emerging showing that cancer patients have significant impairments in cardiorespiratory fitness; for instance, Loewen *et al.*[11] found that the mean VO_{2peak} in 346 presurgical patients with non-small-cell lung cancer (NSCLC) was 15.8 ± 0.43 ml/kg per min, which is equivalent to 36% below the mean VO_{2peak} for age-matched and sex-matched normative data for sedentary individuals. There is also evidence of significant impairment in cancer patient populations that are considered, in general, to have good functional status. For example, in a cohort of 130 patients with operable breast cancer with ‘good’ performance status (KPS ≥70) and normal cardiac function (that is, resting left ventricular ejection fraction ≥50%), 27 months following the completion of primary adjuvant therapy the mean VO_{2peak} was 22% below that of age-matched sedentary healthy women (L. W. Jones, personal communication). Evidence from randomised trials suggests that the observed marked impairment in VO_{2peak} in patients following the completion of therapy may be primarily sustained during adjuvant therapy; for example, 12 weeks of conventional anthracycline–cyclophosphamide neoadjuvant chemotherapy causes a 1.6 ml/kg per min (9.7%) decrease in VO_{2peak} in women with operable breast cancer.[12] In healthy

women, VO_{2peak} typically declines 10% every decade.[13] It is noteworthy that in addition to systemic adjuvant therapy, cancer patients with early stage disease also receive concomitant supportive medications (such as dexamethasone and antiemetics), and these agents may also contribute to observed declines in VO_{2peak}.[14]

Mechanisms of impairment

In non-cancer clinical populations, the causes of reduced cardiorespiratory fitness are often multifactorial with no single organ component of oxygen transport or use being identified as solely responsible.[4] In brief, the causes of exercise intolerance can be classified into three major categories: first, pulmonary limitation (ventilatory and gas exchange limitations); second, cardiovascular limitation (impairment in cardiac and systemic circulation, and haematological parameters); and third, peripheral limitation (abnormalities impacting oxygen conductance and use, and skeletal muscle contraction).[7] Patients diagnosed with cancer are the personification of a clinical population in which multifactorial causes are responsible for reduced cardiorespiratory fitness. Patients with cancer are often older than the general population and commonly present with a diverse range of pulmonary, cardiovascular, and/or musculoskeletal complications that limit exercise tolerance. Furthermore, prior and current treatment with anticancer and/or supportive-care therapies combined with tumour burden, when applicable, is expected to simultaneously impact several organ components in the oxygen cascade.[4] Finally, indirect effects such as increased physical inactivity (deconditioning) will further contribute to marked reductions in cardiorespiratory fitness.[15]

Here we review the potential causes of reduced cardiorespiratory fitness in patients with cancer as organised by the organ components of the oxygen cascade (Table 2). An extensive discussion of the adverse impact of all anticancer and supportive-care therapies in the oncology setting is beyond the scope of this article; therefore, we focus on the effects of conventional cancer therapy (that is, surgery, combination chemotherapy, radiotherapy, and hormone therapy). To date, a paucity of studies has directly investigated the mechanisms of reduced cardiorespiratory fitness in cancer patients; thus, we also draw evidence from clinical studies with extrapolation to the postulated implications on mechanisms governing cardiorespiratory fitness.

Pulmonary limitations

The first step in the oxygen cascade is delivery of oxygen from the environment to the pulmonary capillaries, which is achieved by increasing ventilation to ensure the maintenance of arterial oxygen and carbon dioxide content. The efficiency of the pulmonary system is governed by alveolar ventilation (involving mechanical factors [that is, respiratory muscle function and airway mechanics]) and pulmonary gas exchange (diffusion capacity). Thus, anticancer therapies that adversely impact either of these processes contribute to exercise intolerance. Clearly, the therapy that is most clearly indicated in this regard is surgical resection of lung tissue in patients presenting with thoracic malignancies, because surgery can greatly reduce the maximal alveolar ventilation and reduce surface area for diffusion. The average reduction in VO_{2peak} is 15–20% and 30% after lobectomy and pneumonectomy, respectively. [16,17] However, Hsia *et al.*[18] found that lung diffusion during peak exercise was normal and the upper limit was not approached in patients with NSCLC after pneumonectomy, suggesting that other components of oxygen transport are also responsible for reduced VO_{2peak} in patients with NSCLC. Nevertheless, at least 30% of patients with inoperable NSCLC present with concomitant chronic obstructive pulmonary disease (COPD),[19] as well as extensive tumour burden. Together, these factors adversely impact respiratory muscle mechanics, airway resistance and gas exchange,[20] contributing to dyspnoea and exercise intolerance.

Lung cancer is not the only malignancy where pulmonary limitations may contribute to the reduced cardiorespiratory fitness. Incidental radiation to the lungs in patients receiving upper thoracic radiation, alone or in combination with systemic chemotherapy, for operable breast cancer causes fibrosis and a subsequent reduction in diffusion capacity.[21] To our knowledge, no study has investigated directly the impact of thoracic radiation or chemotherapy-induced pulmonary abnormalities on cardiorespiratory fitness in cancer patients.

Cardiac limitations

Oxygen is transported in the blood to metabolically active tissues via the pumping action of the heart. In response to exercise, heart rate and stroke volume increase to augment cardiac output in an attempt to match peripheral oxygen demand. Therefore, impairments in heart rate response and systolic and/or diastolic function are important contributors to exercise intolerance. Chemotherapy, radiation, and hormone therapy may adversely impact these parameters.

The detrimental effect of different classes of chemotherapeutic agents on cardiac function has been reviewed in detail previously.[22] Anthracycline-containing chemotherapy can cause significant impairments in left ventricular dysfunction, which can ultimately lead to a reduced ejection fraction and overt heart failure.[23,24] Resting left ventricular ejection fraction was a significant predictor of VO_{2peak} in patients with operable breast cancer following the completion of anthracycline-containing adjuvant chemotherapy.[25] Of importance, patients with preserved ejection fraction may have impaired diastolic relaxation and filling.[26] Diastolic function is a significant determinant of VO_{2peak} in healthy individuals[27] and clinical populations, [28] and is also likely to contribute to diminished VO_{2peak} in patients treated with anthracyclines.

Incidental radiation exposure can also cause cardiac abnormalities as myocardial perfusion defects were detected in 50% of patients receiving left-sided radiation for operable breast cancer.[29] The adverse impact of these defects on cardiorespiratory fitness is not known. The effects of hormone suppression (androgen deprivation therapy [ADT], oestrogen receptor antagonists and aromatase inhibitors) on cardiac function and exercise tolerance are also largely unknown. In preclinical work, ADT has been shown to impair cardiac function and cause higher β-myosin heavy chain distribution,[30] and the marked reduction in the bioactivity of oestrogen associated with aromatase inhibitor therapy theoretically raises concerns about the adverse cardiac effects of this therapy class.

Haematological and vascular function

An adequate concentration of haemoglobin molecules in the blood is critical for the transport of oxygen to the metabolically active skeletal muscles. Aetiologies that impact either the production or destruction of red blood cells cause a proportional reduction in arterial oxygen blood content, diminished convective oxygen delivery to the muscle capillary and reduced diffusive oxygen delivery into the muscle cell; all these effects will markedly reduce cardiorespiratory fitness. To varying degrees, all conventional anticancer therapies may cause a decrease in red-blood cell and haemoglobin concentrations through various aetiologies (excessive blood loss, red blood cell destruction or deficient production). Anaemia (haemoglobin concentration <12.0 g/dl and <13.0 g/dl for women and men, respectively) is a frequent complication in the oncology setting, particularly during chemotherapy, occurring in approximately 30–100% of patients.[31] Due to the nature of the Fick Equation,[32] a reduction in haemoglobin concentration will result in a proportional reduction in VO_{2peak} unless there is a compensatory effect in mitochondrial respiration. In healthy individuals, a 14% reduction in haemoglobin content was associated with a 10%

decline in VO_{2peak}.[33] Dolan *et al.*[34] found significant correlations between percent change in VO_{2peak} and haemoglobin levels in women receiving conventional adjuvant chemotherapy for operable breast cancer.

Vascular structure and function has a critical role in regional blood flow control and hence the matching of blood flow to oxygen demand in the working muscles. There are a large number of vasodilatory substances (including, nitric oxide [NO], prostaglandins, endothelium-derived hyperpolarizing factor, adenosine and ATP) that are known to cause arterial vasodilation[35] and likely contribute to exercise hyperaemia. One of the primary vasodilator regulators is NO, which is essential for maintenance of vascular tone and integrity.[36] NO also has a vital role in scavenging free radicals or reactive oxygen species (ROS).[36] Thus, an increase in ROS production can dramatically reduce the beneficial vasodilatory properties of NO, leading to local vasoconstriction or a reduced functional sympatholysis during exercise. Of relevance, locoregional radiotherapy and certain forms of chemotherapy cause a dramatic increase in ROS generation, which can lead to direct endothelial injury, endothelial dysfunction, vascular remodelling and increased arterial stiffness.[37] In terms of locoregional radiotherapy, Beckman *et al.*[37] found that in patients with operable breast cancer, dilatation of the axillary artery exposed to irradiation was significantly impaired compared with the contralateral, non-irradiated artery. In terms of the arterial stiffness, significant increases in aortic stiffness were observed after 4 months exposure to anthracycline-containing chemotherapy.[38]

Skeletal muscle

The final step in the oxygen cascade is the diffusive transport of oxygen from the capillary bed into the muscle cell to the mitochondria to resynthesise ATP. The efficiency of this process is governed by blood flow in the peripheral circulation, transport of oxygen through the muscle cell via myoglobin, and skeletal muscle oxidative capacity. Deficiencies in any of these steps will result in diminished cardiorespiratory fitness, although whether these defects alter VO_{2peak} in cancer patients remains largely unknown. Of the conventional anticancer therapies, there is a clinical consensus that ADT causes a plethora of unfavourable changes in skeletal muscle function including muscle weakness and muscle atrophy,[39] but few, if any, studies have examined whether such abnormalities are associated with reductions in cardiorespiratory fitness. Preclinical work found that doxorubicin caused a reduction in maximal twitch force,[40] impaired relaxation,[41] and significant alterations in gene pathways responsible for regulating skeletal muscle glycolysis and fatty acid oxidation, which was accompanied by a significant reduction in exercise capacity (L. W. Jones, personal communication). Whether these findings translate to the clinical setting has not been investigated.

Certain solid tumours (such as, NSCLC, advanced-stage colorectal cancer and pancreatic cancer) produce a wide variety of proinflammatory cytokines (for example, TNF-α, interleukins and c-reactive protein) leading to a chronic state of low-grade systemic inflammation. Chronic activation of these cytokines are implicated in the pathogenesis of skeletal muscle atrophy and inhibition of muscle regeneration.[42] Levels of proinflammatory cytokines are inversely related to VO_{2peak} in advanced-stage NSCLC.[43]

Sedentary behaviour

Physical inactivity causes maladaptive changes in all organ components of oxygen transport. For example, in the seminal Dallas Bed Rest and Training Study,[44] 3 weeks of bed rest (inactivity) caused significant reductions in cardiac output, oxidative capacity, and muscle cross-sectional area (that is, muscle atrophy), which resulted in an approximately 35% decline in VO_{2peak}. Most cancer patients do not adhere to national exercise

recommendations[45] and can experience significant declines in physical activity levels from pre-to-post diagnosis.[46] Reduced physical activity combined with the adverse effects of anticancer therapy on all components of the oxygen cascade will markedly reduce cardiorespiratory fitness.

In summary, the evidence reviewed here indicates that in most circumstances multiple factors contribute to diminished cardiorespiratory fitness in patients with cancer. Nevertheless, even if impairment in one organ component seems to be a major contributor to exercise intolerance (in a given patient), oxygen transport is an integrative process wherein functional impairment in one organ component is offset by initial adaptive and eventual maladaptive responses in the other oxygen transport components to maintain whole-body homeostatic regulation. [47] As a consequence, the vast majority of patients have marked reductions in cardiorespiratory fitness relative to sex-matched and age-matched normative data.

Clinical importance

A wealth of studies provide convincing evidence of the remarkable ability of cardiorespiratory fitness to predict cardiovascular disease mortality and all-cause mortality in numerous adult populations.[48] Less is known regarding the prognostic importance of cardiorespiratory fitness in patients with cancer. In two studies, in comparison with patients in the lowest fitness categories, higher VO_{2peak} was associated with significantly prolonged survival in patients with NSCLC and metastatic breast cancer; the prognostic value of VO_{2peak} remained unchanged after adjustment for age, gender, and performance status (L. W. Jones, personal communication).[49] Beyond mortality risk-prediction, cardiorespiratory fitness in cancer patients is correlated with select patient-reported outcomes (for example, quality of life and fatigue), biomarkers associated with cancer progression (including metabolic hormones and proinflammatory cytokines), and cardiovascular disease risk factors (such as, blood pressure and lipid profile).[15,25,50] Finally, with marked reductions in cardiorespiratory fitness, some patients are required to exert near maximal or maximal effort to perform normal activities of daily living (such as, climbing stairs and gardening), which impacts functional independence; this issue is becoming a critical consideration as the number of elderly patients with cancer is anticipated to drastically increase over the next two decades.[51]

Efficacy of exercise training

Over the past decade, there has been increased research and clinical interest in the role of exercise training and rehabilitation following a cancer diagnosis both during and following cancer therapy.[52–54]

After treatment cessation

Randomised trials, mostly in women with operable breast cancer, have investigated the safety, feasibility, and efficacy of exercise training in this setting.[52,53] The putative evidence supports the conclusion that structured exercise training is safe (few adverse events), well tolerated (adherence rates >80%), and associated with 10–15% improvements in different measures of cardiorespiratory fitness in studies adopting traditional exercise prescription guidelines (3–5 days per week at 50% to 75% of baseline VO_{2peak} for 12–15 weeks). Patient-reported outcomes including fatigue and quality of life also improved as a result of exercise training following adjuvant therapy.[52,53]

During treatment

Although less well accepted, randomised trials indicate that exercise training—following traditional exercise prescription guidelines—is safe and well tolerated during various conventional therapeutic modalities and can negate the adverse effects of therapy on cardiorespiratory fitness.[52,53] For example, in the largest trial to date,[55] supervised aerobic training or resistance training did not improve VO_{2peak} in women undergoing conventional adjuvant chemotherapy for operable breast cancer. Aerobic training did, however, completely abrogate the significant VO_{2peak} decline (0.5 ml/kg per min) observed in the patients assigned to the non-intervention control group. Similarly, Segal *et al.*[56] reported that although 24 weeks of supervised aerobic training or resistance training was not associated with significant improvements in VO_{2peak} in men with prostate cancer receiving radiation therapy with or without ADT, it did abrogate the significant decline (1.2 ml/kg per min) observed in the control group.

On the basis of available evidence, second-generation studies are currently underway investigating the optimal exercise prescription (including type, frequency and intensity recommendations) to improve cardiorespiratory fitness in patients with cancer.[57–59] First-generation studies investigating the efficacy of exercise training in cancer populations that include patients with advanced-stage disease and those receiving novel anticancer therapeutics are also warranted.

Underlying mechanisms

Aerobic exercise training is widely established as one of the most-effective therapies to improve cardiorespiratory fitness in healthy individuals. Apart from lung diffusion capacity, it improves the reserve capacity of all other components of oxygen transport and use, which collectively lead to favourable improvements in VO_{2peak}.[44] An overview of the demonstrated efficacy of exercise training on the organ components of oxygen transport in non-cancer clinical populations is provided in Table 3. Unfortunately, there is a paucity of data describing whether similar exercise-induced adaptations occur in patients with cancer. As an initial step, we investigated the effects and mechanisms of supervised aerobic training during neoadjuvant chemotherapy, relative to chemotherapy only, in patients with operable breast cancer.[12] Aerobic training during chemotherapy resulted in an 11.8% improvement in VO_{2peak}, while VO_{2peak} declined 9.4% in patients receiving chemotherapy only. No changes in resting left ventricular ejection fraction were observed in either group although haemoglobin concentration significantly declined (to the same extent) in both groups. Aerobic training did improve endothelial function but these favourable adaptations in vascular function are unlikely to account for all of the improvements in VO_{2peak}, suggesting that augmentation of skeletal muscle oxidative capacity or maximal cardiac output were likely responsible. Unfortunately, neither exercise cardiac function nor muscle oxidative capacity was evaluated in this study.[12] Clearly, further mechanistically focused investigations are critical to improve our understanding of the complex nature of exercise-induced cardiopulmonary adaptations during different classes of anticancer therapeutics—such work has tremendous promise and may lead to the prevention and/or mitigation of the emerging adverse cardiovascular and skeletal muscle effects of anticancer therapy.

Exercise prescription

Exercise training for cancer patients both during and following adjuvant therapy is recommended by several agencies.[52,60] In general, these recommendations follow the standard exercise guidelines for healthy individuals— 3–5 days per week for ≥30 min per session for moderate-intensity exercise or 3 days per week for ≥20 min per session for vigorous-intensity exercise. Although general exercise prescription guidelines likely confer

health benefits for all individuals with cancer, exercise should be prescribed on a patient-by-patient basis with consideration of cancer type, therapy, limitations to exercise, and other medical characteristics. To this end, Table 4 provides examples of suggested exercise prescriptions for patients presenting with one of the three major classifications of exercise intolerance. Clearly, before initiation of any exercise program, it is highly advisable for all individuals to undergo appropriate pre-exercise screening; specific tools are available in the oncology setting.[61]

Conclusions

Although the mechanisms remain to be elucidated, emerging evidence suggests that structured exercise training may be an important adjunct for optimal recovery and possibly prevention of therapy-associated exercise intolerance. In addition, our understanding of the molecular mechanisms underlying the purported protective properties of exercise against anticancer therapy-induced cardiovascular injury is virtually non-existent. This major research gap needs to be addressed since elucidation of these complexities will be essential to inform evidence-based exercise guidelines, as well as for the identification of new therapeutic targets to facilitate optimal health, quality of life, and longevity in cancer patients.

From a practical perspective, in contrast to other areas of clinical medicine, exercise training recommendations and/or exercise-based rehabilitation programmes are not part of standard clinical management following a cancer diagnosis. Establishment of such programmes face a number of major obstacles arguably the most important of which, at least in the USA, is that a cancer diagnosis is not considered a qualifying diagnosis for exercise-based rehabilitation by most major insurance companies. Other major hurdles include the requirement to establish programmes with personnel possessing the specialised knowledge of exercise–oncology principles, limited access to specialised services in rural communities, and lack of oncologist referral and support. In terms of the latter hurdle, the initiation of more sophisticated ongoing and forthcoming second-generation exercise– oncology trials will provide further rigorous evidence. However, simply increasing the number and size of trials may be insufficient; for example, despite overwhelming evidence of benefit, referral and adherence rates to exercise- based cardiac rehabilitation programmes remains alarmingly low.[62] To avoid similar issues in the oncology setting, effectiveness-based (implementation) and cost-effectiveness studies together with continued advocacy from the various stake holders (in parallel with efficacy-based trials) is required to ensure wide implementation and uptake of these programmes.

Acknowledgments

L. W. Jones is supported in part by research grants from the National Cancer Institute (CA143254, CA142566, CA138634, CA133895 and CA125458) and funds from George and Susan Beischer.

References

1. Warburton DE, Nicol CW, Bredin SS. Prescribing exercise as preventative therapy. CMAJ. 2006; 174:961–974. [PubMed: 16567757]
2. Jones LW, Peppercorn J. Exercise research: early promise warrants further investment. Lancet Oncol. 2010; 11:408–410. [PubMed: 20434709]
3. Gielen S, Schuler G, Adams V. Cardiovascular effects of exercise training: molecular mechanisms. Circulation. 2010; 122:1221–1238. [PubMed: 20855669]
4. Jones LW, Eves ND, Haykowsky M, Freedland SJ, Mackey JR. Exercise intolerance in cancer and the role of exercise therapy to reverse dysfunction. Lancet Oncol. 2009; 10:598–605. [PubMed: 19482248]

5. Wagner PD. Why doesn't exercise grow the lungs when other factors do? Exerc Sport Sci Rev. 2005; 33:3–8. [PubMed: 15640714]
6. Hoppeler H, Weibel ER. Limits for oxygen and substrate transport in mammals. J Exp Biol. 1998; 201:1051–1064. [PubMed: 9510519]
7. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003; 167:211–277. No authors listed. [PubMed: 12524257]
8. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. Lancet Oncol. 2008; 9:757–765. [PubMed: 18672211]
9. Arena R, et al. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. Circulation. 2007; 116:329–343. [PubMed: 17576872]
10. Palange P, et al. Recommendations on the use of exercise testing in clinical practice. Eur Respir J. 2007; 29:185–209. [PubMed: 17197484]
11. Loewen GM, et al. Preoperative exercise VO_2 measurement for lung resection candidates: results of Cancer and Leukemia Group B Protocol 9238. J Thorac Oncol. 2007; 2:619–625. [PubMed: 17607117]
12. Jones, LW., et al. Effects of aerobic training to improve cardiovascular function and prevent cardiac remodeling after cytotoxic therapy in early breast cancer [abstract]. Proc. American Association for Cancer Research 102nd Annual Meeting; 2011. p. a5024
13. Fleg JL, et al. Accelerated longitudinal decline of aerobic capacity in healthy older adults. Circulation. 2005; 112:674–682. [PubMed: 16043637]
14. Fitzgerald MD, Tanaka H, Tran ZV, Seals DR. Age-related declines in maximal aerobic capacity in regularly exercising vs. sedentary women: a meta-analysis. J Appl Physiol. 1997; 83:160–165. [PubMed: 9216959]
15. Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol. 2007; 50:1435–1441. [PubMed: 17919562]
16. Bolliger CT, et al. Pulmonary function and exercise capacity after lung resection. Eur Respir J. 1996; 9:415–421. [PubMed: 8729998]
17. Nagamatsu Y, et al. Long-term recovery of exercise capacity and pulmonary function after lobectomy. J Thorac Cardiovasc Surg. 2007; 134:1273–1278. [PubMed: 17976462]
18. Hsia CC, Ramanathan M, Estrera AS. Recruitment of diffusing capacity with exercise in patients after pneumonectomy. Am Rev Respir Dis. 1992; 145:811–816. [PubMed: 1554207]
19. Sekine Y, Behnia M, Fujisawa T. Impact of COPD on pulmonary complications and on long-term survival of patients undergoing surgery for NSCLC. Lung Cancer. 2002; 37:95–101. [PubMed: 12057873]
20. Travers J, et al. Mechanisms of exertional dyspnea in patients with cancer. J Appl Physiol. 2008; 104:57–66. [PubMed: 17975124]
21. Marks LB, et al. Physical and biological predictors of changes in whole-lung function following thoracic irradiation. Int J Radiat Oncol Biol Phys. 1997; 39:563–570. [PubMed: 9336133]
22. Yeh ET, et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation. 2004; 109:3122–3131. [PubMed: 15226229]
23. Von Hoff DD, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979; 91:710–717. [PubMed: 496103]
24. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003; 97:2869–2879. [PubMed: 12767102]
25. Jones LW, et al. Cardiovascular risk profile of patients with HER2/neu-positive breast cancer treated with anthracycline-taxane-containing adjuvant chemotherapy and/or trastuzumab. Cancer Epidemiol Biomarkers Prev. 2007; 16:1026–1031. [PubMed: 17507633]
26. Tassan-Mangina S, et al. Tissue Doppler imaging and conventional echocardiography after anthracycline treatment in adults: early and late alterations of left ventricular function during a prospective study. Eur J Echocardiogr. 2006; 7:141–146. [PubMed: 15941672]

27. Vanoverschelde JJ, et al. Contribution of left ventricular diastolic function to exercise capacity in normal subjects. J Appl Physiol. 1993; 74:2225–2233. [PubMed: 8335552]
28. Silvilairat S, Wongsathikun J, Sittiwangkul R, Pongprot Y, Chattipakorn N. Effects of left ventricular function on the exercise capacity in patients with repaired tetralogy of Fallot. Echocardiography. 2011; 28:1019–1024. [PubMed: 21929568]
29. Zeng J, et al. Impact of incidental cardiac irradiation on the development of shortness of breath and changes in pulmonary function tests in patients receiving radiation for lung cancer [abstract 1048]. Int J Radiat Oncol Biol Phys. 2006; 66 (Suppl):S157–S158.
30. Hydock DS, Lien CY, Schneider CM, Hayward R. Effects of voluntary wheel running on cardiac function and myosin heavy chain in chemically gonadectomized rats. Am J Physiol Heart Circ Physiol. 2007; 293:H3254–H3264. [PubMed: 17906105]
31. Grotto HZ. Anaemia of cancer: an overview of mechanisms involved in its pathogenesis. Med Oncol. 2008; 25:12–21. [PubMed: 18188710]
32. Ekblom B, Goldbarg AN, Gullbring B. Response to exercise after blood loss and reinfusion. J Appl Physiol. 1972; 33:175–180. [PubMed: 5054420]
33. Levine BD. VO_{2max}: what do we know, and what do we still need to know? J Physiol. 2008; 586:25–34. [PubMed: 18006574]
34. Dolan LB, et al. Hemoglobin and aerobic fitness changes with supervised exercise training in breast cancer patients receiving chemotherapy. Cancer Epidemiol Biomarkers Prev. 2010; 19:2826–2832. [PubMed: 20861399]
35. Thijssen DH, Green DJ, Hopman MT. Blood vessel remodeling and physical inactivity in humans. J Appl Physiol. 2011; 111:1836–1845. [PubMed: 21737819]
36. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature. 1987; 327:524–526. [PubMed: 3495737]
37. Beckman JA, Thakore A, Kalinowski BH, Harris JR, Creager MA. Radiation therapy impairs endothelium-dependent vasodilation in humans. J Am Coll Cardiol. 2001; 37:761–765. [PubMed: 11693749]
38. Chaosuwannakit N, et al. Aortic stiffness increases upon receipt of anthracycline chemotherapy. J Clin Oncol. 2010; 28:166–172. [PubMed: 19901105]
39. Galvão DA, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int. 2008; 102:44–47. [PubMed: 18336606]
40. Hydock DS, Lien CY, Jensen BT, Schneider CM, Hayward R. Characterization of the effect of *in vivo* doxorubicin treatment on skeletal muscle function in the rat. Anticancer Res. 2011; 31:2023–2028. [PubMed: 21737618]
41. van Norren K, et al. Direct effects of doxorubicin on skeletal muscle contribute to fatigue. Br J Cancer. 2009; 100:311–314. [PubMed: 19165199]
42. Argilés JM, López-Soriano FJ, Busquets S. Mechanisms to explain wasting of muscle and fat in cancer cachexia. Curr Opin Support Palliat Care. 2007; 1:293–298. [PubMed: 18685378]
43. Jones LW, et al. Systemic inflammation, cardiorespiratory fitness, and quality of life in patients with advanced non-small cell lung cancer. J Thorac Oncol. 2008; 3:194–195. [PubMed: 18303444]
44. Saltin B, et al. Response to exercise after bed rest and after training. Circulation. 1968; 38(Suppl):VII1–VII78. [PubMed: 5696236]
45. Blanchard CM, Courneya KS, Stein K. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. J Clin Oncol. 2008; 26:2198–2204. [PubMed: 18445845]
46. Irwin ML, et al. Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. Cancer. 2003; 97:1746–1757. [PubMed: 12655532]
47. Hsia CC. Coordinated adaptation of oxygen transport in cardiopulmonary disease. Circulation. 2001; 104:963–969. [PubMed: 11514387]
48. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ. 2006; 174:801–809. [PubMed: 16534088]

49. Jones LW, et al. Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer. Cancer. 2010; 116:4825–4832. [PubMed: 20597134]
50. Jones LW, et al. Cardiovascular reserve and risk profile of postmenopausal women after chemoendocrine therapy for hormone receptor–positive operable breast cancer. Oncologist. 2007; 12:1156–1164. [PubMed: 17962609]
51. Muss HB, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med. 2009; 360:2055–2065. [PubMed: 19439741]
52. Schmitz KH, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010; 42:1409–1426. [PubMed: 20559064]
53. Speck RM, Courneya KS, Mâsse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and metaanalysis. J Cancer Surviv. 2010; 5:87–100. [PubMed: 20052559]
54. Jones LW, et al. Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis. Oncologist. 2011; 16:112–120. [PubMed: 21212429]
55. Courneya KS, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol. 2007; 25:4396–4404. [PubMed: 17785708]
56. Segal RJ, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol. 2009; 27:344–351. [PubMed: 19064985]
57. Jones LW, et al. The lung cancer exercise training study: a randomized trial of aerobic training, resistance training, or both in postsurgical lung cancer patients: rationale and design. BMC Cancer. 2010; 21:155. [PubMed: 20409311]
58. Jones LW, et al. Rationale and design of the Exercise Intensity Trial (EXCITE): A randomized trial comparing the effects of moderate versus moderate to high-intensity aerobic training in women with operable breast cancer. BMC Cancer. 2010; 10:531. [PubMed: 20925920]
59. Christensen JF, et al. Progressive resistance training and cancer testis (PROTRACT)–efficacy of resistance training on muscle function, morphology and inflammatory profile in testicular cancer patients undergoing chemotherapy: design of a randomized controlled trial. BMC Cancer. 2011; 11:326. [PubMed: 21806789]
60. Kushi LH, et al. American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin. 2006; 56:254–281. [PubMed: 17005596]
61. Jones LW. Evidence-based risk assessment and recommendations for physical activity clearance: cancer. Appl Physiol Nutr Metab. 2011; 36:S101–S112. [PubMed: 21800938]
62. Gravely-Witte S, et al. Effects of cardiac rehabilitation referral strategies on referral and enrollment rates. Nat Rev Cardiol. 2010; 7:87–96. [PubMed: 19997077]
63. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 7. Lippincott Williams and Wilkins; Philadelphia: 2006.

Key points

- Cardiorespiratory fitness is governed by the integrative capacity of the pulmonary and cardiovascular systems and skeletal muscle to transport and use oxygen to resynthesise ATP
- Patients with cancer have marked reductions in cardiorespiratory fitness due to impairments in one or more organs in the transport or use of oxygen as a result of anticancer therapy and effects secondary to therapy
- Emerging evidence indicates that cardiorespiratory fitness might be a robust predictor of prognosis following a cancer diagnosis
- Cardiorespiratory fitness level assessment might be an important tool to assess treatment tolerability in patients prior to therapy initiation
- Randomised trials indicate that exercise training is a safe and efficacious adjunct therapy to recover and/or prevent cancer therapy induced impairments in cardiorespiratory fitness
- Exercise should be prescribed on a patient-by-patient basis with consideration for cancer type, therapy, personal limitations and other medical characteristics

Review criteria

A comprehensive literature review using PubMed, MEDLINE, Sport Discus, and Cochrane Controlled Trials Register (1966 to January 2012) was conducted using the following MESH terms and text words: ‘exercise’, ‘cardiorespiratory fitness’, ‘exercise capacity’, ‘cardiopulmonary fitness’, ‘functional capacity’, ‘exercise test’, ‘oncology’, and ‘cancer’. Relevant reference lists were also hand-searched.

Table 1

Cardiorespiratory fitness testing modalities

Characteristic	Maximal		Submaximal	
	Cardiopulmonary exercise testing	**Stress test**	**Age-predicted HR test**	**6 or 12 min walk test**
Direct measurement of VO_2	Yes	No	No	No
Estimated measurement of VO_2	No	Yes—estimated from highest workload achieved during the test	Yes—estimated from the workload achieved at a predefined HR (70–85% HR_{max})	Yes—estimated from BP and HR response during test
Equipment	Expired gas measurement system Electronically-braked cycle ergometer or motorised treadmill 12-lead ECG Pulse oximeter BP monitoring	Electronically-braked cycle ergometer or motorised treadmill 12-lead ECG Pulse oximeter BP monitoring	Electronically-braked cycle ergometer or motorised treadmill HR monitor Pulse oximeter BP monitoring 12-lead ECG (optional but recommended) Stop watch	30m corridor HR monitor Pulse oximeter Stop watch
Duration	8–12min	8–20min	8–20min	6 or 12 min
Description	Incremental exercise with expired gas analysis until volitional exhaustion or symptom limitation	Incremental exercise until volitional exhaustion or symptom limitation	Incremental exercise until predefined HR (70–85% HR_{max}) achieved	Participant asked to walk as far as possible in 6 or 12 min
Purpose	Intervention Non-intervention Exercise limitation Diagnosis (CVD) Prognosis Measurement of cardiorespiratory fitness	Intervention Non-intervention Diagnosis (CVD) Measurement of cardiorespiratory fitness	Non-intervention	Intervention Non-intervention Prognosis
Patient population	Operable (early stage) Inoperable (advanced stage) Undergoing therapy Off therapy Pre-surgery Pre-BMT	Operable (early stage) Inoperable (advanced stage) Undergoing therapy Off therapy	Operable (early stage)	Inoperable (advanced stage) Undergoing therapy Frail, elderly

Abbreviations: BMT, bone-marrow transplantation; BP, blood pressure; CVD, cardiovascular disease; ECG, echocardiogram; HR, heart rate; HR_{max}, heart rate maximum; VO_2, oxygen consumption.

Table 2

Proposed mechanisms of impaired cardiorespiratory fitness in patients with cancer

Organ component of oxygen system	Oxygen transport component	Tumour and/or cancer therapy-associated impairment					At-risk cancer patient population
		Tumour presence	Surgery	Chemotherapy	Radiation	Hormone suppression	
Pulmonary	Reduced diffusion capacity Increased alveolar hypoventilation Pulmonary vascular damage, remodelling, and fibrosis	Primary or secondary lung cancer (↑↑↑)	Thoracic surgery (↑↑↑)	Platinum-based chemotherapy (↑) Other classes (unknown)	Thoracic radiation (↑↑)	Unknown	Primary or secondary thoracic malignancies Presenting with concomitant respiratory disease Any population receiving thoracic or total-body irradiation
Cardiac	Left ventricular systolic dysfunction Reduced left ventricular relaxation Reliance on late rather than early filling Reduced ventricular compliance Reduced stroke volume Reduced cardiac output Reduced chronotropic reserve Reduced myocardial perfusion	NA	NA	Anthracycline-based chemotherapy (↑↑↑) Other classes (↑↑)	Thoracic radiation (↑↑)	ADT (↑) Endocrine therapy (unknown)	Any population receiving chemotherapy particularly anthracycline-containing regimens Presenting with concomitant cardiovascular disease or cardiovascular risk factors Any population receiving thoracic or total-body irradiation Elderly patients (>65 years)
Blood	Reduced haemoglobin concentration	Haematological malignancy (↑↑↑)	Extensive surgery (↑↑↑)	All classes (↑↑↑)	Femur exposure (↑)	Unknown	The majority of cancer patients receiving any type of

Organ component of oxygen system	Oxygen transport component	Tumour and/or cancer therapy-associated impairment					At-risk cancer patient population
		Tumour presence	Surgery	Chemotherapy	Radiation	Hormone suppression	
		Extensive bone metastases (↑↑)					anticancer therapy
Vascular function	Impaired vasodilatory response to hyperaemia (that is, endothelial dysfunction) Increased arterial stiffness Increased reactive oxygen species or decreased anti-inflammatory expression	NA	NA	Anthracycline-based chemotherapy (↑) Other classes (unknown)	Thoracic radiation (↑)	Unknown	Any population receiving chemotherapy particularly anthracycline-containing regimens Presenting with concomitant cardiovascular disease or cardiovascular risk factors Any population receiving thoracic or total-body irradiation
Skeletal muscle oxidative capacity	Muscle atrophy Reduced capillarisation Reduced enzymes for oxidative phosphorylation Reduced mitochondrial density Reduced myoglobin concentration Fiber type transition to more glycolytic phenotype	Advanced disease (↑↑↑)	NA	Anthracycline-based chemotherapy (↑) Other classes (unknown)	Muscle- implicated radiation (unknown)	Unknown	Any population receiving chemotherapy, particularly anthracycline-containing regimens Patients experiencing cachexia Prolonged bed-rest (for example, post BMT) Presenting with concomitant cardiovascular disease or respiratory disease

Abbreviations: ↑, weak evidence; ↑↑, moderate evidence; ↑↑↑, strong evidence; ADT, androgen deprivation therapy; BMT, bone marrow transplantation; NA, not applicable.

Table 3

Efficacy of exercise training to augment oxygen transport organ components in clinical populations

Oxygen transport component	Evidence in non-cancer clinical patients	Evidence in cancer patients
Pulmonary	Increased diffusion capacity (–) Reduced expiratory obstruction (–) Reduced pulmonary vascular damage, remodelling, and fibrosis (–)	Not available
Cardiac	Increased left ventricular systolic function (↑↑) Increased left ventricular relaxation (↑↑) Improvements in early filling (↑↑) Increased ventricular compliance (↑↑) Increased stroke volume (↑↑↑) Increased cardiac output (↑↑↑) Increased chronotropic reserve (↑↑) Increased myocardial perfusion (↑)	Not available
Blood	Increased haemoglobin concentration (↑↑↑)	Haemoglobin concentration (–)
Vascular function	Improved endothelial function (↑↑↑) Reduced arterial stiffness (↑↑) Reduced reactive oxygen species or increased anti-inflammatory expression (↑↑↑)	Improved endothelial function (↑) Reduced reactive oxygen species or increased anti-inflammatory activity (↑)
Skeletal muscle oxidative capacity	Increased muscle mass (↑↑↑) Increased capillarisation (↑↑↑) Increased enzymes for oxidative phosphorylation (↑↑↑) Increased mitochondrial density (↑↑↑) Increased myoglobin concentration (↑) Fibre type transition to more fatigue resistant type IIA fibre (↑↑↑)	Increased muscle mass (↑↑)

Abbreviations: –, no change; ↑, weak evidence; ↑↑, moderate evidence; ↑↑↑, strong evidence.

Table 4

Exercise prescription guidelines for cancer patients

Patient characteristics (examples)	Goal of exercise	Initial prescription	Exercise progression
General (patients following the completion of adjuvant therapy for localised disease presenting with no overt underlying comorbid disease)	To improve all components of the oxygen cascade	Frequency: 3–5 days/week Intensity: * light to moderate Type: aerobic endurance Time: 20–40min/session	Frequency: 4–6 days/week Intensity: * light to vigorous Type: aerobic endurance, interval training and resistance Time: ~30–60min/session
Cardiovascular limitation (patients presenting with chemotherapy-induced LV dysfunction and/or anaemia)	Improved LV filling and relaxation, enhanced LV compliance, improvement in endothelial function, and decreased arterial stiffness	Frequency: 3 days/week Intensity: * light to moderate Type: aerobic endurance Time: ~20–30min/session	Frequency: 3–5 days/week Intensity: * moderate Type: aerobic Time: ~20–60min/session
Respiratory limitation (patients following pulmonary resection with concomitant COPD)	Reduced ventilatory demand and dyspnoea, with favourable skeletal muscle adaptations	Frequency: 3–4 days/week Intensity: * light to moderate Type: aerobic endurance and resistance Time: >20min/session	Frequency: 4–5 days/week Intensity: * moderate to vigorous Type: aerobic endurance, interval and resistance Time: ~20–60min/session
Peripheral limitation (patients presenting with tumour and/or treatment-induced cachexia or muscle atrophy)	Increased muscle mass and aerobic enzymes, and improved fibre type transition and oxidative metabolism	Frequency: 3 days/week Intensity: ≠ light to moderate Type: resistance Time: 20–30min/session	Frequency: >3 days/week Intensity: ≠ moderate Type: resistance and aerobic Time: ~20–60min/session

* Relative intensities guideline for aerobic endurance training: light (light effort, normal or slight breathing, 40–50% of measured heart rate maximum or VO_{2peak}); moderate (moderate effort, elevated breathing, 50–70% of measured heart rate maximum or VO_{2peak}); vigorous (hard effort, greater breathing, >70% of measured heart rate maximum or VO_{2peak}).

≠ Relative intensities guideline for resistance training: light (50–60% of measured one repetition maximum), moderate (60–80% of measured one repetition maximum), and hard (>80% of measured one repetition maximum).[63]

Abbreviations: COPD, chronic obstructive pulmonary disease; LV, left ventricular; VO_{2peak}, peak oxygen consumption.