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Cardio-oncology (MG Fradley, Section Editor)

# Exercise Training for Cancer Survivors

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## Opinion statement

Cardiovascular diseases are a common cause of morbidity and mortality in cancer survivors. Furthermore, some cancer therapies are now being increasingly recognized to have negative cardiovascular effects, or cardiotoxicity. Exercise therapy has been found to improve cardiorespiratory fitness in patients with cancer as well as attenuate the cardiotoxic effects of cancer therapy. It is the centerpiece for cardiac and pulmonary rehabilitation programs. It is also an important component in cardio-oncology rehabilitation. Exercise is generally safe, and its benefit is observed when started as soon as the diagnosis of cancer and throughout cancer survivorship.

## Introduction

With advancement in cancer screening and treatment, there are growing numbers of cancer survivors. Cardiovascular diseases (CVD) are the leading non-cancer cause of morbidity and mortality in cancer survivors today [1]. The risk factors of cancer and CVD commonly overlap, such as increasing age and unfavorable lifestyle such as smoking, obesity, and alcohol misuse [2]. Cardiorespiratory fitness (CRF), typically measured as $VO_{2peak}$, is a strong predictor of all-cause mortality [3] and cancer survival [4]. CRF often deteriorates during cancer therapy and may not recover after completion of therapy [5–7]. For instance, the CRF for patients with breast cancer was 27% lower than their age-matched sedentary healthy counterparts in one study. The CRF was reduced further to 31% lower than sedentary healthy controls during primary adjuvant chemotherapy [6]. Reduction of CRF was also found in patients with gynecologic cancer [8] and in survivors of pediatric cancer [9]. These findings suggest that CRF reduction may not only affect patients receiving therapy with known cardiotoxicity

(e.g., patients with breast cancer receiving anthracyclines) but all patients along the cancer survivorship spectrum.

Commonality of risk factors for cancer and CVD allows for a similar approach in prevention, such as lifestyle modification and exercise prescription. Exercise prescription is an essential component in cardiac and pulmonary rehabilitation. In the oncology population, exercise has been shown to reduce cancer recurrence by 48% and cancer mortality by 27% [10]. Given the growing evidence of improved cardiovascular outcomes associated with exercise in patients with cancer, the American Heart Association has recently published a position statement recommending comprehensive multimodality cardio-oncology rehabilitation (CORE), which includes structured exercise programs [11].

## Cancer and cardiovascular disease

The risk factors for developing CVD and cancer are similar. These include advanced age, suboptimal diet, obesity, tobacco use, diabetes mellitus, and physical inactivity. Physical activity guidelines for the general population recommend at least 150 min of moderate-intensity aerobic physical activity per week [12]. Physical inactivity (< 150 min/week) as compared with those who exercise for > 150 min per week is shown to be associated with increased risk of CVD and breast cancer. In the INTERHEART study, it was observed that increasing activity level is associated with lower incidence of CVD [13]. Studies have also demonstrated lower breast cancer risk in women who are more physically active [14]. It has been proposed that physical activity may reduce insulin-related factors and inflammation, which in turn decrease breast cancer risk [15]. Given the commonality in risk factors for CVD and cancer, and the high prevalence of mortality and morbidity of CVD in cancer survivors, exercise is an important part of a comprehensive risk factor management program to lower CVD and cancer risks.

## Cancer therapy and cardiotoxicity

Multiple cancer therapies are now recognized to be cardiotoxic; associated toxicities may include accelerated atherosclerosis, conduction system disorders, cardiac dysrhythmias, and cardiomyopathy. Anthracyclines, such as doxorubicin and epirubicin, are commonly used in breast cancer treatment. This class of therapy intercalates with DNA and interferes with replication, which causes cell death. Anthracyclines are associated with irreversible LV dysfunction. The cardiotoxic effect of anthracyclines is thought to be mediated by direct toxicity causing myocyte cell death and via oxygen radicals which accelerate myocyte death [16–18]. Cardiotoxicity mediated by anthracyclines can happen during or after treatment. The risk of cardiotoxicity rises with cumulative doses of anthracyclines [19–21].

Monoclonal antibodies, such as trastuzumab, are another class of breast cancer therapeutic agent which is known to cause LV dysfunction. These agents inhibit HER2 signaling. However, unlike doxorubicin, trastuzumab-induced LV dysfunction is largely reversible [22]. The risk factors for trastuzumab-associated cardiomyopathy include hypertension, diabetes, history of anthracycline use, and increasing age [23].

Patients with underlying cardiovascular risk factors are at higher risk of anthracycline cardiotoxicity [19–21]. These observations may be explained by the "multi-hit hypothesis." For instance, underlying CVD or risk factors may cause initial clinical or subclinical insult to the myocardium. The use of cancer therapy with

potential cardiotoxicity further increases the risk of development of clinical cardiotoxicity [24, 25].

Given the potential for development of cardiotoxicity with cancer therapies, patients' underlying cardiovascular risk factors should be optimized to minimize the compounding cytotoxic effect.

# Exercise and cardiorespiratory fitness

Exercise therapy has been shown to improve cardiorespiratory fitness in multiple studies. The exercise regimens studied were quite diverse, including aerobic exercise, mixed aerobic and resistance training, supervised and home-based exercise, and high-intensity (40 to 80% peak heart rate, heart rate reserve, or $VO_{2peak}$ determined from cardiopulmonary exercise test) and low-intensity (25 to 40% of heart rate reserve) exercises. The heterogeneity of exercise regimens studied has been attributed as a potential reason for differing degrees of improvement in cardiorespiratory fitness.

# Impact of exercise therapy throughout cancer survivorship

## Between cancer diagnosis and cancer therapy

Exercise therapy before initiation of cardiotoxic therapy, or so-called "prehabilitation," has been demonstrated to be beneficial in pre-clinical studies. In mouse models, doxorubicin-treated groups demonstrate decline in cardiac mitochondrial function and increased oxidative stress [26–28]. Exercise has been shown to protect against doxorubicin-induced cardiac tissue and mitochondrial negative remodeling [29–32], and the benefit extends to exercise initiated prior to cardiotoxic therapy initiation [33].

Clinical data for prehabilitation are more scant. A case study reported the beneficial effect of prehabilitation in a patient with breast cancer [34]. The patient received aerobic training starting 1 week prior to chemotherapy (regimen not specified) and continued for 8 weeks (which overlapped with 2 cycles of chemotherapy). There was improvement in the patient's fatigue symptoms and functional ability. However, robust evidence on the effect of prehabilitation for patients with cancer who are going to undergo cardiotoxic therapy is currently unavailable. Nevertheless, it is postulated that prehabilitation may improve baseline functional capacity before cardiotoxic therapy and may enhance exercise therapy compliance. The benefits of prehabilitation may be seen in cancer patients who are not receiving anthracycline chemotherapy, as well. In one study, patients with colorectal cancer undergoing surgery were randomized to prehabilitation (exercise therapy 4 weeks prior to surgery) or rehabilitation (exercise immediately after surgery), with home-based moderate-intensity aerobic and resistance exercises in addition to nutritional counseling and relaxation techniques. Patients in the prehabilitation group were found to have improved functional capacity compared with the rehabilitation group at 8 weeks post-surgery [35].

## Exercise during cancer therapy

Studies have demonstrated improvement in CRF with exercise therapy during cancer treatment. A seminal trial by MacVicar and colleagues studied the effect of 3 times per week aerobic exercise on functional capacity in patients with stage II

breast cancer receiving non-anthracycline-based chemotherapy over a 10-week period. Aerobic exercise with intensity between 60 and 85% of heart rate reserve was shown to improve functional capacity by 40% as compared with usual care [36]. Similarly, in another study, both home-based low-intensity exercise and supervised moderate–high-intensity resistance and aerobic exercise program attenuated CRF decline (– 9% vs – 17%) in patients with breast cancer receiving adjuvant chemotherapy [37]. Both exercise groups reported less symptoms such as nausea/vomiting and pain, as well as better social functioning as compared with the non-exercised group. Furthermore, the moderate–high-intensity combination exercise group had better muscle strength, physical fitness levels, and cognitive function as compared with the low-intensity exercise and control groups [37]. McNeely and colleagues [38] reported an increase in $VO_{2peak}$ by 3.39 mL/kg/min with exercise (including aerobic, and mixed aerobic and resistance) compared with usual care in their meta-analysis of 3 studies including 95 patients with early-stage breast cancer. The OptiTrain study investigated the effects of a 16-week aerobic and mixed aerobic and resistance exercise programs on the physical and mental health in patients with breast cancer undergoing chemotherapy as compared with usual care [39]. At 2 year follow-up, the group who underwent aerobic exercise was found to have lower overall cancer-related symptoms and the group who underwent mixed aerobic and resistance training had lower cancer-related fatigue and higher muscle strength [40].

The effect of a tailored, nonlinear aerobic exercise regimen has also been studied. As opposed to linear aerobic training, where the exercise volume increases with time, nonlinear exercise program adjusts training load (both increases and decreases) throughout the training period. A supervised, nonlinear, 3 times per week program, consisting of 30–45 min of ergometry exercise at 60–100% $VO_{2peak}$ for 12 weeks, was shown to improve CRF in patients with early-stage breast cancer receiving adjuvant chemotherapy [41]. In addition, nonlinear aerobic exercise also increased brachial artery flow-mediated dilatation, which reflected an improvement in endothelial function [41].

As in patients with breast cancer, exercise during cancer therapy is also beneficial in patients with prostate cancer and lymphoma. In patients with prostate cancer receiving radiotherapy with or without androgen deprivation therapy, both aerobic and resistance exercises improved CRF compared with usual care [42]. A supervised 12-week aerobic exercise program also improved CRF by 17% in patients with lymphoma receiving chemotherapy (agents not specified) as compared with a 2% decline in CRF with usual care; benefits were observed immediately after exercise intervention as well as at 6-month follow-up [43]. In addition to CRF, exercise also improved patients' overall quality of life, fatigue symptoms, mood, and lean body mass [43]. A meta-analysis including 571 patients with lymphoma and prostate, breast, and colon cancer revealed a significant increase in $VO_{2peak}$ by 2.90 mL/kg/min with exercise (including aerobic, resistance training, and both high- and low-intensity aerobic trainings) as compared with a significant decline in $VO_{2peak}$ by 1.02 mL/kg/min in the control group [44]. In a larger meta-analysis of 48 randomized controlled trials which included 3632 patients with cancer (1900 in exercise group, 1642 in control group), exercise was associated with an increase of $VO_{2peak}$ by 2.80 mL/kg/min as compared with 0.02 mL/kg/min in the control group [45]. The exercise regimens included aerobic exercise, or mixed aerobic and resistance training, with the majority being supervised.

However, despite the beneficial effects observed in other cancer populations, exercise may not attenuate the cardiotoxic effects of trastuzumab. In an observational study, patients with HER-2-positive breast cancer treated with adjuvant trastuzumab received aerobic exercise therapy 3 times per week for the first 4 months [46]. Compared with baseline, the resting left ventricular ejection fraction (LVEF) at the end of the study was found to have decreased significantly during trastuzumab therapy [46]. However, the study was limited by the overall adherence rate to exercise of only 59% and the relatively short-term follow-up period [46]. As well, the outcomes were compared with patients' baseline and there was no non-exercised control group [46].

There appears to be conflicting evidence regarding the beneficial effect of exercise during cancer therapy. However, this may be due to different exercise regimens, different patient population, and different cancer therapies administered. Patient adherence to exercise therapy may also contribute to differing impact of exercise therapy. Nevertheless, the majority of studies supported that exercise therapy during cancer therapy appeared to improve CRF, quality of life, and vascular endothelial function compared with usual care.

## Exercise after cancer therapy

Exercise exposure after cancer treatment appears to improve cardiovascular outcomes and all-cause mortality in patients with cancer. Observational data suggested that higher physical activity level (≥ 9 MET hours/week) as compared with 0 MET hours/week is associated with a 7% absolute risk reduction (12.2% vs 5.2%) in cardiovascular events in adult survivors of childhood Hodgkin lymphoma [47]. This study also found that a higher activity level was associated with a lower cardiovascular event risk in a dose-dependent manner [47]. Similarly, in patients with non-metastatic breast cancer, after a median follow-up period of 8.6 years, cardiovascular event incidence decreased with increasing activity level, with an adjusted hazard ratio of 0.65 for breast cancer survivors with activity level of ≥ 24.5 MET hours/week compared with those with < 2 MET hours/week [48]. Adherence to national exercise guidelines with activity of ≥ 9 MET hours/week was associated with a 23% decrease in cardiovascular events [48].

Randomized controlled trials have demonstrated improvement in CRF with exercise training that was started after cancer therapy. In postmenopausal breast cancer survivors who had received surgical therapy, chemotherapy, and/or radiation therapy, aerobic exercise with ergometry 3 times per week for 15 weeks was shown to improve CRF by 15% and quality of life compared with a control group [49]. Similarly, Rogers and colleagues reported improvement of CRF with a 12-week structured multidisciplinary rehabilitation including aerobic exercise program and discussion groups in patients with ductal carcinoma in situ or stages I to IIIa breast cancer as compared with those receiving usual care [50]. Home-based, moderate-intensity aerobic exercise was also found to improve CRF by 20% in patients who had completed therapy for colorectal cancer compared with no change in CRF in patients receiving usual care [51].

The benefit of exercise after cancer therapy may also extend beyond improvement in CRF. In testicular cancer survivors, high-intensity interval aerobic exercise was found to increase CRF by 3.7 ml O2/kg/min, improve

modifiable cardiovascular risk factors, and improve vascular function (reduced arterial thickness and stiffness) [52]. Conversely, nonlinear aerobic exercise of 24 weeks was also reported to improve CRF in patients with prostate cancer, but with no change in cardiovascular risk factors such as lipid levels, body habitus, and blood pressure readings. In an observational study, the impact of a 3-month home-based exercise was evaluated in long-term survivors of childhood leukemia who were treated with anthracycline with preserved ejection fraction and diastolic dysfunction. Compared with a matched cohort, those in the exercise group had significant improvement in diastolic function (measured by diastolic mitral inflow velocity E and E′) [53].

Overall, exercise therapy appears to improve CRF in cancer survivors after cancer therapy. However, there are conflicting evidence regarding its beneficial effect on cardiovascular risk factors.

A summary of the studies investigating the impact of exercise therapy throughout cancer survivorship discussed in this article is shown in Table 1.

*AT*, aerobic training; *RT*, resistance training; *UC*, usual care; *wk*, week; *RCT*, randomized controlled trial; *ADT*, androgen deprivation therapy; *HF*, heart failure

## Safety of exercise program

A meta-analysis of 48 trials studying the impact of exercise on CRF in patients with cancer reported 44 adverse events. The majority of adverse events were dizziness, chest pain, and musculoskeletal pain. Rare adverse events included hip fracture and myocardial infarction [45]. Aerobic exercise was also reported to be safe in patients with metastatic breast cancer [54]. However, the attendance rate was moderate (63%), and 27% of patients discontinued their exercise program permanently. Reasons for discontinuation included disease progression, pain, and amotivation. In patients who were able to tolerate aerobic exercise, their CRF and functional capacity had improved [54].

Although exercise therapy is generally safe in patients with cancer, exercise may cause more adverse events in the subset of patients with advanced heart failure. In a post-hoc substudy of the HF-ACTION study, in which patients with stable NYHA II–IV heart failure and LVEF ≤ 35% were randomized to aerobic training or usual care, aerobic training was not associated with improved clinical outcomes among the subset of patients with a history of cancer, and an increased risk of death and hospitalization was observed in those patients who were unable to adhere to prescribed exercise regimens. [55]. These findings contradict those reported in the overall HF-ACTION study which reported a non-significant reduction in all-cause mortality and hospitalization in patients with heart failure [56]. Caution should be used in interpreting these results, as it was a post-hoc analysis and patients with cancer accounted for only 3.8% of the overall study cohort. This observation does, however, highlight the need for pre-exercise screening and individualized exercise programs in this complex population.

**Table 1. Studies investigating the effect of exercise therapy throughout cancer survivorship**

| Study | *N* | Type | Population | Intervention | Outcomes |
|---|---|---|---|---|---|
| Before cancer therapy | | | | | |
| De Paleville et al. (2007) [34] | 1 | Case study | 42 year-old woman with new breast cancer diagnosis | AT 1 wk prior to and 8 wk into chemotherapy | Improved fatigue and functional ability |
| Gillis et al. (2014) [35] | 77 | RCT | Patients with non-metastatic colorectal cancer scheduled for curative resection | Moderate AT and RT 4 weeks prior to surgery (prehab) or immediately following surgery (rehab) | Better CRF by 6-min walk test in prehab vs rehab group |
| During cancer therapy | | | | | |
| MacVicar et al. (1989) [36] | 45 | RCT | Patients receiving chemotherapy for stage II breast cancer | 10-wk AT vs stretching vs UC | AT improved CRF by 40% vs other groups |
| Van Waart et al. (2015) [37] | 230 | RCT | Patients receiving adjuvant chemotherapy for breast or colon cancer | Supervised AT + RT vs home AT vs UC | Supervised AT + RT: – 17% CRF<br>Home AT: – 9% CRF<br>UC: – 18% CRF |
| Wengstrom et al. (2017) [39] | 240 | RCT | Patients receiving chemotherapy for breast cancer | 16-wk AT vs mixed AT + RT vs UC | AT lower symptoms<br>AT + RT lower fatigue |
| Segal et al. (2009) [42] | 121 | RCT | Patients receiving radiotherapy with or without ADT | 24-wk AT vs RT vs UC | Improved CRF (RT + 0.5%, AT + 0.1% vs UC – 5%). AT and RT improved fatigue; RT improved QoL, aerobic fitness, upper and lower body strength |
| Courneya et al. (2009) [43] | 122 | RCT | Patients receiving treatment for lymphoma | 12-wk supervised AT vs UC | AT improved CRF + 17% vs UC – 2% |
| Scott et al. (2018) [54] | 65 | RCT | Patients with metastatic breast cancer | 12-wk AT vs stretching | Unchanged CRF in AT vs stretching |
| After cancer therapy | | | | | |
| Jones et al. (2014) [47] | 90 | Retrospective cohort | Patients with treated childhood Hodgkin lymphoma | ≥ 9 MET h/wk vs < 9 METS h/wk | CV events: ≥ 9 MET h/wk: 51% less in any CV event |
| | 2973 | | | Physical activity | Adjusted HR vs < 2 MET h/wk: |

**Table 1.** (Continued)

| Study | *N* | Type | Population | Intervention | Outcomes |
|---|---|---|---|---|---|
| Jones et al. (2016) [48] | | Prospective cohort | Patients with non-metastatic breast cancer | | 2 to 10.9 MET h/wk: 0.91 (0.76–1.09)<br>11 to 24.5 MET h/wk: 0.79 (0.66–0.96)<br>≥ 24.5 MET h/wk: 0.65 (0.53–0.80) |
| Courneya et al. (2003) [49] | 53 | RCT | Patients with breast cancer after treatment | 15-wk supervised AT vs UC | AT improved CRF by 15%, no change in UC |
| Rogers et al. (2015) [50] | 222 | RCT | Patients with breast cancer after treatment | 12-wk supervised + unsupervised AT vs UC | AT improved CRF by 12% vs UC increased by 10% (not statistically significant) |
| Pinto et al. (2013) [51] | 46 | RCT | Patients with colorectal cancer after treatment | 3-month supervised + 4–12-month unsupervised AT vs UC | AT improved CRF by 32% vs improved 15% with UC |
| Adams et al. (2017) [52] | 63 | RCT | Patients with testicular cancer | 12-wk supervised AT vs UC | AT improved CRF by 11% and carotid distensibility by 16% vs no change with UC |

## Implementation of exercise prescription

The American Cancer Society and The American College of Sports Medicine recommend 150 min per week of moderate-intensity exercise or 60–75 min per week of vigorous intensity exercise, or an equivalent combination of the two. Despite the overall positive impact of exercise on cancer survivors, approximately one-third of cancer survivors adhere to the physical activity recommendation, compared with the 50% adherence level in the healthy population [57].

Rehabilitation often centers around a multidisciplinary approach addressing lifestyle modification, exercise prescription, optimizing cardiac risk factors, and psychosocial concerns. The American Heart Association has published a scientific statement introducing CORE which includes nutrition counseling, weight management, smoking cessation, psychosocial support, cardiovascular risk factor modification (blood pressure, cholesterol, diabetes management), physical activity counseling, and exercise therapy [11]. The statement also identifies patients who are at high risk of experiencing cardiotoxicity and may benefit most from CORE, including

patients receiving high-dose anthracycline or radiation therapy, low-dose anthracycline or trastuzumab with cardiac risk factors, or both anthracycline and trastuzumab [11].

The American Heart Association recommends 3 sessions per week of 30–60 min of aerobic exercise at 70–80% at peak heart rate, determined by an exercise treadmill test. This recommendation can serve as a general approach to exercise prescription to all cancer survivors. However, it is not patient-specific and may not consider the decrease in heart rate reserve due to chemotherapy-related autonomic dysfunction [58]. Exercise therapy can then be implemented in a tailored, nonlinear fashion, in which the intensity and duration of exercise is adjusted (increased or decreased) between sessions [41]. Exercise training typically begins with an adaptation phase of moderate-intensity aerobic exercise. Thereafter, the training moves to a progression phase, in which high-intensity exercise is introduced [59]. The intensity of exercise and number of repetitions change in order to avoid training fatigue. This approach may mitigate potential under- or overdosing of exercise therapy that can occur with exercise therapy based on percentage of peak heart rate. Given the heterogeneity of natural history and therapies used in different cancer types, as well as potentially increased adverse events with exercise in high-risk patients with heart failure, a tailored and multidisciplinary approach to exercise prescription should be taken. This relies on strong collaboration between oncologists, cardiologists, and exercise physiologists.

Exercise therapy settings may include supervised, unsupervised, community, or home-based models. Flexibility in exercise therapy delivery may maximize patient participation. Higher-risk patients may benefit from supervised, hospital, or community-based exercise therapy programs, while lower-risk patients may participate in unsupervised, home-based programs. For instance, community-based, supervised exercise program such as the LIVESTRONG program at has demonstrated physical and psychological improvements in cancer survivors [60].

## Barriers to implementation

Despite the growing evidence supporting exercise therapy in cancer survivors, there are challenges to patient participation and therapy implementation. Patients with cancer often have competing priorities and commitments (personal, medical appointments, etc.) which may hinder their participation in exercise programs. Furthermore, cancer- and treatment-related symptoms, such as profound fatigue, limit patients' ability to participate. Lack of physician endorsement through offering exercise programs and referrals may also decrease patient participation in exercise therapy [61]. In order to maximize the benefits derived from exercise therapy, patients should be referred to exercise or rehabilitation programs as early as possible in the continuum of cancer survivorship. The lack of standardized, objective risk stratification systems also makes it difficult for referring providers to identify and triage patients who would most benefit from exercise therapy. Development of such stratification systems (via clinical phenotypes, biomarkers, genomics, or artificial intelligence) may allow for precise, targeted exercise prescriptions. As patients with cancer

have different comorbidities and various treatments which have different side effect profiles, individualized programs may mitigate patient-specific barriers to attending exercise therapies.

## Future directions

The beneficial effect of exercise in cancer survivors is increasingly recognized. There are still many knowledge gaps with respect to the different effects of exercise at various points on the cancer survivorship continuum. There are currently no randomized data regarding the impact of exercise therapy on cancer recurrence. Trials are currently underway to evaluate how exercise would influence progression-free survival in patients with ovarian cancer (LIVES trial) [62], disease-free survival in patients with colon cancer (CHALLENGE trial) [63], and overall survival in patients with metastatic castrate-resistant prostate cancer (INTERVAL trial) [64]. Furthermore, large studies investigating the effect of exercise on cancer survivors beyond CRF are limited. Studies are underway to determine the effects of multidisciplinary team interventions including exercise training in the prevention of LV remodeling in patients treated with anthracyclines and trastuzumab (TITAN trial) [65]. More research is needed to further elucidate the effects and types of exercise regimen on different cardiovascular outcomes and measurements in patient with various types and treatment of cancer.

## Summary

With advancement of cancer therapy, there are now increasing numbers of cancer survivors. Cardiovascular conditions are now the most common non-cancer-related cause for mortality and morbidity. In addition, cancer therapy may be associated with cardiotoxicity. Exercise therapy has been demonstrated to improve fitness and may mitigate the negative impact of cancer therapy on the cardiovascular system throughout the spectrum of cancer survivorship. Exercise therapy is best delivered in a multidisciplinary setting, together with an individualized approach, in order to maximize the cardiovascular benefit in patients with different types of cancer and therapies. Future studies are currently underway to determine the effect of exercise on cancer survivorship beyond functional and cardiovascular outcomes.

## Compliance with Ethical Standards

**Conflict of interest**
Calvin K.W. Tong, Benny Lau and Margot Davis declare that they have no conflict of interest.

**Human and animal rights and informed consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance


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