Exercise, cancer and cardiovascular disease: what should clinicians advise?
Allison Zimmerman, Maria Isabel Camara Planek, Catherine Chu, Opeyemi Oyenusi, Agne Panerc, Kerryn Reding, Jamario Skeetee, Brian Clark and Tochi M. Okwuosa

Cardiovascular disease is one of the leading causes of morbidity and mortality in persons with cancer. The elevated risk is thought to derive from the combination of cardiovascular risk factors and direct cardiotoxicity from cancer therapies. Exercise may be a potential strategy to counteract these toxicities and maintain cardiovascular reserve. In this article, we review the evidence for the potential cardioprotective effects of exercise training in cancer patients before, during, and following treatment. We also propose a patient-tailored approach for the development of targeted prescriptions based on individual exercise capacity and cardiovascular reserve. Cardiovasc Endocrinol Metab 10: 62–71 Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Introduction
The relationship between cancer therapy and cardiovascular disease (CVD) is well-recognized. This is in part due to some chemotherapeutic agents being inherently toxic to cardiac cells (cardiotoxic), a phenomenon driven by cellular injury and cardiac myocytes’s susceptibility to damage compounded by its very limited regenerative capacity. Unfortunately, this makes the cardiovascular system (CVS) particularly vulnerable to irreparable damage when exposed to certain agents used in the treatment of cancer [1]. While much of the current research on the impact of cancer therapy on the CVS focuses on changes to the heart, cancer therapy (including chemo and radiation therapy) also affects oxygen utilization by the body. Specifically, exposure to various chemotherapeutic regimens produces declines in cardiovascular function and reserve, as can be seen with findings of decreased peak oxygen consumption uptake (peak VO2) in patients post-chemotherapy [2,3]. Additionally, cardiorespiratory fitness (CRF), a global measure of cardiovascular function, declines between 5 and 26% during exposure to cancer therapy, and may remain depressed even after cessation of treatment [2,4].

Notably, there is an emerging paradigm of involvement of the cardiovascular-skeletal muscle axis in CRF in cancer patients [5]. This is corroborated by data suggesting that cancer survivors may experience decrements in skeletal muscle quality in addition to cardiovascular decrements which together contribute to CRF [6,7]. It is clear that rehabilitation focused on improving cardiovascular function has the potential to mitigate damage from cancer therapy and improve patient outcomes. However, the extent to which these programs should focus on muscle quality is yet unclear. While exercise therapy and cardiac rehabilitation are recommended and mainstay for many cardiac and pulmonary conditions, this strategy is not routinely offered to cancer patients despite a growing body of evidence that indicates these patients would likely see cardiovascular benefit from exercise [8]. Here, we review the current evidence exploring the impact of exercise on cardiovascular outcomes in adults with cancer, and propose a framework for targeted exercise prescription in this population.

Utilizing multiple approaches, several studies have been conducted to explore the impact of exercise on cardiac outcomes in subjects with cancer. These predominantly involve examining variables such as the timing of introduction of exercise, whether initiated pre- or post-cancer diagnosis/treatment, and include both animal and human subject studies.

Impact of exercise before cancer treatment on preventing future cardiovascular outcomes
As noted, certain cancer treatments may result in profound damage to the CVS. Until recently, only animal studies had examined whether exercise in the period before cancer diagnosis alters subsequent risk of cardiovascular events.
Exercise has been shown to improve cardiovascular outcomes in patients with cancer even when initiated before the diagnosis of cancer. This was demonstrated in a recent large prospective observational cohort study (the first human study of its kind) which showed that higher levels of physical activity before cancer diagnosis were associated with lower risks of CVEs in women with breast cancer [15]. Using cardiovascular endpoints such as heart failure, myocardial infarction, angina, coronary revascularization, peripheral and coronary artery disease, transient ischemic attack, stroke, and death; exercise was shown to be beneficial in this cohort. Specifically, the study demonstrated that individuals with high levels of physical activity, defined as those in the top quartile of physical activity levels before the diagnosis of cancer, had significantly lower risk of future composite CVEs [hazard ratio (HR): 0.63, 95% confidence interval (CI) 0.45–0.88, \( P = 0.02 \)] as well as death secondary to coronary heart disease (HR: 0.41, 95% CI 0.21–0.78, \( P < 0.01 \)) when compared to their counterparts with lower levels of physical activity before diagnosis of cancer. Not only does this study provide added incentive to encourage exercise in the general population but acts as a basis to better define whether this observed benefit is present when exercise is initiated after diagnosis of cancer in previously inactive individuals.

Taken together, these studies provide support for stronger consideration for exercise as primordial and primary prevention to mitigate cardiovascular risks associated with cancer and cancer therapy. It is therefore suggested that typical cardiovascular risk management in cancer patients should be pursued in the same manner or more aggressively as with the general population [16].

Exploring the safety and efficacy of exercise in patients undergoing cancer treatment

Several recent reviews have concluded that exercise in patients with cancer is not only safe, but also improves quality of life, improves aerobic fitness, reduces risk of cancer recurrence, and reduces risk of all-cause mortality [8,17–20]. Specifically, while results have been widely variable, exercise studies during cancer treatment suggest that overall, exercise diminishes cancer treatment-associated decline and improves cardiovascular outcomes.

The randomized controlled trials (RCTs) examining exercise during treatment are summarized in Table 1 and have variable findings, likely due to the heterogeneous nature of these studies as elaborated further. First, there is a lack of standardization in the utilized methodologies and measured outcomes in these studies. For instance, most clinical studies examining this topic during treatment focus on changes in aspects of CRF and peak \( VO_2 \) rather than clinically relevant outcomes such as reductions in functional status or mortality. Furthermore, the methods used to define CRF are not standardized throughout clinical reviews and often do not consider factors such as age, comorbidities and baseline functional status, all of which are established to have a strong impact on CRF. Similarly, there is inconsistency in exercise specific variables such as the exercise dosing regimen, \( VO_2 \), and metabolic equivalent targets. To overcome these inconsistencies in methodologies, standardized guidelines by which age-specific CRF categories are defined have been recently proposed [21].

Second, there is paucity of robust clinical data on the effects of exercise during cancer treatment on CVD outcomes such as subclinical reductions in left ventricular ejection fraction (LVEF), ischemic CVD events, and cardiovascular mortality [8]. For instance, a noteworthy study by Haykowsky et al. examined the effect of aerobic training (AT) on 17 women with HER2-positive breast cancer during the first 4 months of adjuvant trastuzumab therapy. They found that despite exercise, initiation of trastuzumab was associated with LV cavity dilation and reduced LVEF (pre: 64 ± 4% versus post: 59 ± 4%, \( P < 0.05 \)). While the findings might suggest that the benefit of exercise might be absent in preventing changes in LVEF post-exposure to trastuzumab, this might be a premature conclusion, given the small population size and absence of a control group [22]. As such, large scale research is on-going to better assess the impact of exercise on improving cardiovascular outcomes in patients during cancer therapy.

The ongoing Multidisciplinary Team Intervention in Cardio-Oncology (TITAN) and Exercise to prevent AnthraCycline-based Cardio-Toxicity seek to integrate exercise into treatment plans for cancer patients [23,24]. TITAN specifically will assess cardiac remodeling with imaging and biomarkers at 6–12 months follow-up from supervised to independent exercise training with Cardiology team support in breast or lymphoma patients receiving chemotherapy [24]. The Optimal Training Women with Breast Cancer Trial RCT has a
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>N</th>
<th>Cohort, setting</th>
<th>Baseline CVD</th>
<th>Cardiotoxic cancer therapies</th>
<th>Modal, intensity, frequency (day/week), duration (weeks)</th>
<th>Cardiovascular outcomes</th>
<th>Protocol adherence LTF %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacVicar et al. (1989) (25)</td>
<td>45</td>
<td>Breast cancer patients: AT, stretching, UC</td>
<td>NR</td>
<td>Adjuvant CT</td>
<td>VO₂p</td>
<td>AT: 40% increase</td>
<td>LTF: 27%</td>
</tr>
<tr>
<td>Segal et al. (2001) (26)</td>
<td>123</td>
<td>Breast cancer patients: AT, self-directed AT, UC</td>
<td>NR</td>
<td>Previous XRT: 37%</td>
<td>VO₂p (estimated)</td>
<td>Supervised: 2.4% increase</td>
<td>LTF: 27%</td>
</tr>
<tr>
<td>Kim et al. (2006) (27)</td>
<td>41</td>
<td>Breast cancer patients: AT, UC</td>
<td>None</td>
<td>AT: 8.3% increase</td>
<td>UC: 2.1% increase</td>
<td>P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Courneya et al. (2007) (28)</td>
<td>242</td>
<td>Breast cancer patients: AT, RT, or UC</td>
<td>NR</td>
<td>Taxane CT: 31%</td>
<td>VO₂p</td>
<td>AT: 0.2% increase</td>
<td>LTF: 9%</td>
</tr>
<tr>
<td>Daley et al. (2007) (29)</td>
<td>108</td>
<td>Breast cancer patients: AT, UC</td>
<td>None</td>
<td>Exercise</td>
<td>VO₂p</td>
<td>AT: 93%</td>
<td>LTF: 9%</td>
</tr>
<tr>
<td>Courneya et al. (2009) (30)</td>
<td>122</td>
<td>Lymphoma patients: AT or UC</td>
<td>HTN 29% DLD 30%</td>
<td>CT: % NR</td>
<td>VO₂p</td>
<td>AT: 17% increase</td>
<td>LTF: 11%</td>
</tr>
<tr>
<td>Segal et al. (2009) (31)</td>
<td>121</td>
<td>Prostate cancer: AT, RT, UC</td>
<td>NR</td>
<td>XRT; % NR</td>
<td>VO₂p</td>
<td>AT: 0.1% increase</td>
<td>LTF: 7%</td>
</tr>
<tr>
<td>Courneya et al. (2013) (32)</td>
<td>301</td>
<td>Breast cancer patients: AT, high-dose AT, combined AT/RT</td>
<td>Obese 23%</td>
<td>Taxane: 74.1% Trastuzumab: 16.6%</td>
<td>VO₂p</td>
<td>AT: 12% decrease</td>
<td>LTF: 7%</td>
</tr>
<tr>
<td>Jones et al. (2013) (33)</td>
<td>20</td>
<td>Breast cancer patients: AT, UC</td>
<td>NR</td>
<td>Neoadjuvant CT</td>
<td>VO₂p</td>
<td>AT: 13% increase</td>
<td>LTF: 5%</td>
</tr>
<tr>
<td>Samuel et al. (2013) (34)</td>
<td>48</td>
<td>Head and neck cancer patients: AT or RT, UC</td>
<td>CT: % NR</td>
<td>AT: 3–5/10 perceived exertion</td>
<td>VO₂p</td>
<td>AT: 42 m increase</td>
<td>Adherence not measured</td>
</tr>
<tr>
<td>Study (year)</td>
<td>N</td>
<td>Cohort, setting</td>
<td>Baseline CVD</td>
<td>Cardiotoxic cancer therapies</td>
<td>Modality, intensity, frequency (day/week), duration (weeks)</td>
<td>Cardiovascular outcomes</td>
<td>Protocol adherence LTF %</td>
</tr>
<tr>
<td>-------------</td>
<td>---</td>
<td>-----------------</td>
<td>-------------</td>
<td>-----------------------------</td>
<td>-------------------------------------------------</td>
<td>---------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Hornsby et al. (2014)</td>
<td>20</td>
<td>Breast cancer patients: AT, UC</td>
<td>NR</td>
<td>Neoadjuvant doxorubicin + cyclophosphamide</td>
<td>CE, Moderate to high intensity, 3 days/week, 12 weeks</td>
<td>VO₂₉, AT: 13.3% increase, UC: 8.6% decrease</td>
<td>82% NR</td>
</tr>
<tr>
<td>Moller et al. (2015)</td>
<td>45</td>
<td>Breast and colon cancer patients: hospital or home-based intervention versus UC</td>
<td>NR</td>
<td>Neoadjuvant CT</td>
<td>Home: walking with pedometer, Hospital: bikes, resistance and circuit training, dance</td>
<td>Peak VO₂ decreased across study groups, LTF 12%</td>
<td>NR</td>
</tr>
<tr>
<td>Van Waart et al. (2015)</td>
<td>230</td>
<td>Breast or colon cancer patients: home supervised AT, CT, UC</td>
<td>NR</td>
<td>Adjuvant CT</td>
<td>Home AT: 12–14 Borg Score, XRT: 78%</td>
<td>Estimated exercise capacity, UC: 18% decrease</td>
<td>NR LTF: 11%</td>
</tr>
<tr>
<td>Gilbert et al. (2016)</td>
<td>50</td>
<td>Prostate cancer: Exercise, UC</td>
<td>Prior MI: 8%, Angina: 12%, HTN: 64%, HTN since ADT: 12%</td>
<td>Androgen deprivation therapy</td>
<td>CE, TM, row, 55–75% max HR, 3 days/week, 12 weeks</td>
<td>FMD of the brachial artery, P &lt; 0.001</td>
<td>93% NR</td>
</tr>
<tr>
<td>Scott et al. (2018)</td>
<td>65</td>
<td>Breast cancer patients with metastatic disease: AT, stretching (control)</td>
<td>HTN, DLD, DM, or CAD: 34%</td>
<td>CT: 57%</td>
<td>55–100% VO₂p, 3 days/weeks, 12 weeks</td>
<td>VO₂₉, AT and control: P = NS</td>
<td>NR LTF: 3%</td>
</tr>
</tbody>
</table>

Bold value indicates statistically significant of P values.

ADT, androgen deprivation therapy; AT, aerobic training; CE, cycle ergometer; CT, chemotherapy; CVD, cardiovascular disease; DLD, dyslipidemia; ET, elliptical training; FMD, flow-mediated dilatation; HR, hazard ratio; HRR, heart rate reserve; HTN, hypertension; LTF%, lost to follow-up percent; NC, no change; NR, not reported; NS, non-significant; RCT, randomized controlled trial; RM, resistance maximum; RT, resistance training; TM, treadmill; UC, usual care; VO₂₉, peak oxygen consumption; XRT, radiation therapy.

*Supervised unless otherwise stated.
longer follow up of 5 years; and via personalized exercise prescriptions, aims to compare AT and combined resistance training to usual care in breast cancer patients, with CRF as a secondary endpoint. So far, at 2-year follow-up, there has been no statistically significant difference in pre-specified outcomes between exercise and usual care control groups [39]. Nonetheless, a recent protocol has been proposed for a systematic review of the effectiveness of exercise in counteracting cardiotoxicity related to anticancer therapies in women with breast cancer. The proposed primary outcomes for this review include systolic function, diastolic function, and myocardial deformation imaging outcomes [40].

Despite the variations in baseline characteristics across the existing studies on this subject, the overall, results are promising and suggest that exercise during cancer treatment improves cardiovascular health (Table 1), and therefore act as a basis for supporting the call for structured exercise therapy for patients with cancer.

The impact of exercise initiated post-cancer treatment

There is some evidence that exercise improves CRF even when initiated after the completion of cancer therapy. Compared to clinical studies exploring the impact of exercise when started before or during cancer treatment, findings surrounding the post-treatment phase are somewhat mixed. However, while several studies suggest no difference in CRF measured by VO₂ in exercise regimens after cancer treatment, the majority of studies point towards efficacy in post-treatment exercise (Table 2) [41,42].

Similar to clinical studies focusing on exercise during treatment, there are a few notable studies that have assessed the effects of exercise when initiated after completion of cancer therapy using parameters beyond CRF/VO₂. Notably, a recent RCT by Adams et al. [43] was the first to provide evidence that high-intensity AT on testicular cancer patients post-treatment improved not only CRF, but other variables such as also arterial thickness, Framingham risk score, arterial stiffness, and low-density lipoprotein (P < 0.01).

On the other hand, two recent RCTs demonstrated mixed benefit of exercise post-cancer treatment in this population. Jones et al. [33] showed that exercise produced increases in VO₂ peak, which was associated with improved vascular endothelial function, with no changes in LVEF. Similarly, a recent retrospective intention-to-treat analysis of the Efficacy and Safety of Exercise Training in Patients with Chronic Heart Failure (HF-ACTION) RCT showed that in patients with cancer who have heart failure and randomized to AT had a cardiovascular mortality reduction compared to the usual care group (HR 1.94; CI 1.12–3.16; P = 0.02) [44]. It is notable that although mortality reduction was observed in this study, VO₂ improvement was not, which contrasts with what is seen in the general population, in which VO₂ has the strongest predictive ability for future mortality [45]. This raises the possibility that VO₂ may not be a sufficiently sensitive outcome in the assessment of exercise effect on cardiovascular health in cancer patients despite being the most frequently utilized outcome measure in clinical trials as seen in Tables 1 and 2. It also speaks to the potential presence of alternate mechanisms by which exercise might confer cardiovascular benefit in this population.

Regarding the type of exercise, recently, a RCT by Scott et al. [46] examined patients with primary breast cancer patients who had completed cancer treatment. In this study, patients were randomized to linear AT, non-linear AT, or usual care. Here, linear prescription of exercise defined as having fixed-dosing (per week) and fixed intensity for all patients revealed only modest improvement in CRF independent of dosing of chemotherapy. Of note, this study reported substantial heterogeneity in the response to both linear and non-linear AT in this population of breast cancer survivors with impaired CRF. The authors concluded that exercise programs of greater amount or length, as prescribed in their non-linear programs, may be needed to produce meaningful improvements among this population of post-treatment breast cancer patients [46].

In summary, there is yet insufficient but increasing evidence to conclude that non-linear AT and better-tailored exercise post-cancer treatment improves cardiovascular health. Additional studies are needed to examine the impact of specific approaches to individually-tailored exercise interventions on a variety of outcomes in cancer survivors.

Clinical guidelines and recommendations

Based on current evidence, clinical guidelines recommend moderate-intensity exercise–both aerobic and resistance training–for patients with cancer both during and after treatment. This recommendation also applies to intense cancer treatments such as stem cell transplantation [47,48]. However, such linear exercise recommendations in cancer patients and survivors are fraught with specific problems. For example, the determination of moderate-intensity exercise recommendation may be confounded by the presence of sequelae of cancer therapies, such as autonomic dysfunction due to cisplatin or external radiation therapy; or via medications used to treat cardiac complications of chemotherapy such as beta-blockers [49]. Additionally, it is important to consider that there will be significant differences in exercise tolerability due to considerable variability in baseline clinical status such as differences in treatments received, cardiovascular risk factors, and physiologic status (below or comparable to age- and sex-matched VO₂peak) [50].
Additional evidence suggests that generalized exercise recommendations might not be appropriate for all patients with cancer. For example, a study by Jones et al. [44], showed that cardiovascular mortality and hospitalization was significantly higher in patients with heart failure and a history of cancer when randomized to aerobic exercise compared to the patients with heart failure and history of cancer assigned to guideline-based usual care. As such, standardized exercise prescription may not be appropriate in this population given the significant potential for patient variability. Based on this, we recommend an individualized approach to exercise recommendations in patients with cancer (Fig. 1).

To determine which patients with cancer might safely tolerate exercise before, during or post-chemotherapy, exercise stress testing may be a worthwhile risk stratification tool. Specifically, exercise stress testing and can identify

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>N</th>
<th>Cohort, setting</th>
<th>Baseline CVD</th>
<th>Timing after treatments</th>
<th>Modality, intensity, frequency, duration</th>
<th>Cardiovascular outcomes</th>
<th>Protocol adherence LTF %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courneya et al. (2003) (51)</td>
<td>53</td>
<td>Breast cancer patients: AT, UC</td>
<td>NR</td>
<td>14 months after CT</td>
<td>CE, 70–75% VO₂</td>
<td>VO₂p AT: 15% increase</td>
<td>NR LTF: 6%</td>
</tr>
<tr>
<td>Thorsen et al. (2005) (42)</td>
<td>139</td>
<td>Breast, gynecological, lymphoma, testicular cancer: unsupervised AT, UC</td>
<td>NR</td>
<td>30 days after therapy</td>
<td>TM, CE, skiing 3 days/weeks 15 weeks</td>
<td>VO₂p AT and UC: P = 0.001</td>
<td>NR LTF: 20%</td>
</tr>
<tr>
<td>Daley et al. (2007) (29)</td>
<td>108</td>
<td>Breast cancer patients: AT, UC</td>
<td>None</td>
<td>Post therapy</td>
<td>1:1 specialized AT 65–85% max HR 3 days/week 8 weeks</td>
<td>Aerobic fitness score AT versus UC P = 0.002</td>
<td>NR</td>
</tr>
<tr>
<td>Courneya et al. (2013) (32)</td>
<td>301</td>
<td>Breast cancer patients: AT, high dose AT, UC</td>
<td>None</td>
<td>Post-treatment</td>
<td>CE, ET, TM, row 55–75% VO₂ 3 days/week Ending 3–4 post-CT</td>
<td>High dose AT superior to AT and UC P = 0.03</td>
<td>NR</td>
</tr>
<tr>
<td>Jones et al. (2014) (44)</td>
<td>90</td>
<td>HF patients with cancer: 3 months supervised + 4–12 months unsupervised AT, UC</td>
<td>HTN: 94% DM: 38% HF: 100%</td>
<td>Post-HF therapy</td>
<td>CE, TM 60–70% HRR 4 days/week 52 weeks</td>
<td>VO₂p AT: 4% Increase</td>
<td>NR LTF: 14%</td>
</tr>
<tr>
<td>Jones et al. (2014) (52)</td>
<td>50</td>
<td>Prostate cancer patients: AT, UC</td>
<td>HTN: 54% HPL: 60%</td>
<td>75 days after therapy</td>
<td>TM 55–100% speed at VO₂p 5 days/week 24 weeks</td>
<td>VO₂p AT: 9% P = 0.05</td>
<td>79% LTF: 8%</td>
</tr>
<tr>
<td>Rogers et al. (2015) (41)</td>
<td>222</td>
<td>Breast cancer patients: supervised or unsupervised AT, UC</td>
<td>DM: 16% CVD: 8% Low CRF: 100% HTN: 11%</td>
<td>54 months after therapy</td>
<td>CE, ET, TM 40–59% HRR 3–5 days/week 12 weeks</td>
<td>VO₂p AT: 12% increase UC: 10% increase</td>
<td>NR LTF: 2%</td>
</tr>
<tr>
<td>Adams et al. (2017) (43)</td>
<td>63</td>
<td>Testicular cancer patients: supervised AT, UC</td>
<td>Obese: 21% Pre-HTN: 19% Metabolic syndrome: 19% Mild carotid plaque: 57% Moderate-severe carotid plaque: 24%</td>
<td>8 years after therapy</td>
<td>TM 75–95% VO₂p 3 days/week 12 weeks</td>
<td>VO₂p AT: 11% Increase</td>
<td>98% LTF: 3%</td>
</tr>
<tr>
<td>Scott et al. (2020) (46)</td>
<td>174</td>
<td>Postmenopausal breast cancer patients: LET, NLET, AC</td>
<td>Impaired VO₂p</td>
<td>2.6 years after therapy</td>
<td>VO₂p LET: 0.6 ± 1.7 mLO₂/kg·min NLET: 0.8 ± 1.8 mLO₂/kg·min → both compared to AC P = 0.01</td>
<td>Intention-to-treat analysis, regardless of adherence</td>
<td></td>
</tr>
</tbody>
</table>

Bold value indicates statistically significant of P values.

AC, attention control; Control group; AT, aerobic training; CE, cycle ergometer; CRF, cardiorespiratory fitness; CT, chemotherapy; CVD, cardiovascular disease; DM, diabetes; ET, elliptical training; HPL, hyperlipidemia; HR, hazard ratio; HRR, Heart rate reserve; HTN, hypertension; LET, linear, fixed-dose regimen; LTF, lost to follow up; NC, no change; NLET, nonlinear, variable dose regimen; NR, not reported; RCT, randomized controlled trial; RM, resistance maximum; RT, resistance training; TM, treadmill; UC, usual care; VO₂p, peak oxygen consumption; XRT, radiation therapy.

*Supervised unless otherwise stated.
individuals unlikely to tolerate the recommendations for moderate-intensity exercise based on submaximal and maximal exercise reached [53,54]. For example, among deconditioned patients, standardized functional and sub-maximal exercise testing heart rate and blood pressure responses can be used to prescribe exercises of varying intensities independent of disease severity or baseline fitness status [55].

On the other hand, exercise prescriptions that are determined by baseline physiologic endpoints in the absence of up-to-date objective determination of exercise capacity, are at increased susceptibility of underdosing or overdosing exercise therapy. For example, in primary breast cancer patients with autonomic dysfunction and decreased heart rate reserve, the use of standardized age-predicted maximum heart rate may result in exercise overdosing [49].

To date, no organization has reached a consensus on the impact of cancer therapies on overall CVD risk. However, the American Society of Clinical Oncology has provided evidence-based guidelines regarding selected therapies that predispose cancer patients to CVD. The guideline recommends that those who should be considered at increased CVD risk include: (1) treatment with high-dose anthracycline therapy, high dose radiation therapy (when the heart is included in the treatment field), or low dose anthracycline therapy in combination with low dose radiotherapy; Treatment with low-dose anthracycline or trastuzumab alone plus the presence of two or more risk factors (smoking, hypertension, diabetes mellitus, obesity, dyslipidemia, age greater than 60 years at time of treatment, or the presence of compromised cardiac function); Treatment of low-dose anthracycline followed by trastuzumab.

**In settings where CPET unavailable investigators can use maximal incremental exercise tolerance testing (ETT) to determine workload and peak exercise heart rate. CPET, cardiopulmonary exercise testing.**
Another strategy to determine exercise capacity before
prescribing exercise therapy in patients with cancer is
cardiopulmonary exercise testing (CPET). CPET-based
metabolic and ventilatory responses allow for the gener-
ation of 3 to 5 different exercise intensity zones and pro-
vides information on the patient’s VO₂peak, thus providing
data for individualized tailoring of exercise training [57].
Beyond prediction of exercise tolerability, CPET can be
repeated after training to objectively measure and docu-
ment improvement in cardiac fitness and refine training
levels. This is supported by a systematic review which
found that CPET is a safe, noninvasive method to mea-
Sure cardiopulmonary fitness in cancer patients both dur-
ing and after treatment [58]. As discussed, VO₂ may not
be the most appropriate method for assessing exercise effect
on cardiovascular health in cancer patients; nonetheless,
it is the most constructive method currently available
for assessing exercise needs. We therefore recommend
formal CPET in addition to clinical risk stratification to
guide moderate-intensity recommendations (Fig. 1). In
settings where CPET is unavailable, investigators may
use maximal incremental exercise tolerance testing as the
next (although suboptimal) alternative to determine
workload and peak exercise heart rate [59].

Finally, we recommend exercising in a group or super-
vising setting. Data suggest greater and more consist-
ent benefit with exercise interventions that occurred in
group settings compared with individual settings [44,60–
62]. A supervised setting can provide more motivation
for patients and lend initial educational components
to ensure that professionals have the opportunity to
review how to perform exercises safely with the patient.
Exercise prescriptions should be delivered by the
American College of Sports Medicine/American Cancer
Society-certified exercise trainers. Fitness trainers should
be encouraged as much as possible to learn about specific
cancer diagnoses and treatments rendered. They should
be included as part of the medical team, as a diagnosis of
cancer can affect multiple parts of the body, and treat-
ments are becoming increasingly customized.

Future directions
In this review of exercise in the care of cancer patients,
we proposed an algorithm to risk stratify cancer patients
and develop a personalized approach to exercise imple-
mentation. Transition from the research setting to wide-
spread clinical availability presents significant challenges
including lack of staff education on the complexities
involved in the overall health and management of cancer
patients. The effects of cancer stage, treatment type, and
patient-specific risk factors should be clarified when iden-
tifying periods of greatest physical decline and recovery.
Exercise programs will require infrastructures that ena-
ble them to provide services uniquely aligned with expo-
sures and needs of cancer patients. The responsibility of
identifying and referring patients with cancer at risk for

cardiac dysfunction to exercise programs remains in the
hands of both cardiologists and oncologists. Cardiologists
have traditionally worked with oncologists to care for can-
cer patients after cardiac toxicity has occurred, and a pro-
active stance between specialties is pivotal to developing
cardi-oncologic exercise-based rehabilitation.

Further work is needed to demonstrate the benefits of
exercise in producing a reduction in cardiac dysfunction in
the cancer population and to generate guidelines to help
shape referrals and reimbursements. Reimbursement
for cardiac rehabilitation was first established in 1982 for
patients that experienced myocardial infarctions, coro-
nary artery bypass graft surgery, and stable angina [48].
Unfortunately, there is currently no reimbursement stra-
egy available in the USA that can provide patients with
access to exercise-based cardiac rehabilitation programs
on the bases of their malignancy and associated poten-
tially cardiotoxic treatment. With further research and the
development of formal guidelines, exercise-based car-
diac rehabilitation has the potential to provide a widely
accessible comprehensive program that has the potential
to be significantly beneficial to cancer patients across the
United States, regardless of treatment phase.

Conclusion
Persons with cancer, particularly those receiving certain
chemotherapeutic agents are at heightened risk of devel-
oping cardiovascular sequela which can be measured
using a number of outcomes. There is convincing evi-
dence that exercise whether performed before, during,
or following cancer treatment can mitigate these risks.
As such a patient-tailored, supervised, exercise program
using predictions of exercise capacity from stress test-
ing or CPET, is likely to maximize the benefit of this
approach and assist in the prevention of poor cardiovas-
cular outcomes in patients with cancer.

Acknowledgements
Conflicts of interest
There are no conflicts of interest.

References
1 Lenneman CG, Sawyer DB. Cardio-oncology: an update on cardiotoxicity
2 Jones LW, Courneya KS, Mackey JR, et al. Cardiopulmonary function and
age-related decline across the breast cancer survivorship continuum. J Clin
3 Squires RW, Shultz AM, Herrmann J. Exercise training and cardiovas-
4 Huria A, Jones L, Muss HB. Cancer treatment as an accelerated aging


Permission: Editorial staff. Registration: Copyright Clearance Center. Copyright © 2020 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.


