Tailored exercise as a protective tool in cardio-oncology rehabilitation: a narrative review

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Summary
Cardiovascular disease is the leading cause of long-term morbidity and death among cancer survivors, after second malignancies. Preventing cancer treatment-induced cardiotoxicity (CTC) constitutes a crucial endpoint in oncology, from oncology treatment implementation. The American Association of Clinical Oncology has recently highlighted the role of physical exercise as an essential component of co-adjuvant cancer treatment and cancer survivor care programs. Exercise training may protect from cardiotoxicity on a molecular and physiological basis. Two major types of training in this field are: cardiovascular and resistance/strength training. Little is known about the effects of these modalities of exercise on CTC. This narrative review aimed to gather evidence and extract conclusions about the effectiveness of exercise training on CTC. To do so, we reviewed scientific literature under a sophisticated approach in line with the PRISMA project guidelines. Studies on physical training exercise effects and cardiac-related measures throughout the cancer stages (cancer treatment and survivorship) were selected. Data collection comprised extracting information of study features, exercise training characteristics and related effects. As a result, 1087 studies were retrieved from database search and 33 studies were selected, comprising 2778 participants. Most of the studies (n=29) examined the effects of cardiovascular training on CTC. No studies analysed the effects of resistance-based training. We observed a lack of systematic effect of exercise across studies due to the high heterogeneity (e.g., many studies did not follow the guidelines for training interventions in cancer settings). However, studies combining both cardiovascular and resistance components showed promising results. To sum up, higher adherence to clinical guides should be encouraged to implement physical exercise interventions in medical settings and to ensure intervention effectiveness. Moreover, personnalized protocols and routines should be implemented in Cardio-Oncology Rehabilitation Units. Finally, it is mandatory to avoid physical inactivity in patients with cancer.

Key words:

Ejercicio individualizado como herramienta protectora en la rehabilitación cardio-oncológica: revisión narrativa

Resumen
La patología cardiovascular es la primera causa de morbilidad y muerte entre los pacientes supervivientes de cáncer, después de segundas neoplasias. La prevención de cardiotoxicidades inducidas por tratamientos oncológicos constituye una meta en la Oncología. La Asociación Americana de la Oncología Clínica recientemente ha destacado la importancia del ejercicio físico como componente co-adyuvante esencial en el tratamiento contra el cáncer. El ejercicio físico puede dar protección en la cardiotoxicidad desde un punto de vista molecular y fisiológico. Dos tipos de entrenamiento destacan: entrenamiento cardiovascular y de fuerza. Esta revisión pretende recoger evidencia y extraer conclusiones sobre la efectividad del ejercicio físico ante la cardiotoxicidad. Para ello revisamos la literatura científica bajo criterios PRISMA. Estudios basados en el efecto del ejercicio físico y mediciones cardiacas a lo largo de procesos oncológicos (tratamiento oncológicos y supervivientes) fueron seleccionados. Como resultado, 1087 estudios fueron recuperados y 33 estudios fueron seleccionados, comprendiendo 2778 sujetos. La mayoría de los estudios (n=29) examinaron el efecto del entrenamiento cardiovascular en la cardiotoxicidad. No hubo estudios que analizaran exclusivamente el entrenamiento de Fuerza. Observamos una escasez de efecto sistémico a lo largo debido a la alta heterogeneidad. De cualquier modo, los estudios combinando entrenamiento cardiovascular y de fuerza parecen demostrar resultados prometedores. En resumen, las guías clínicas deberían animar a implementar programas de ejercicio físico en el entorno médico y garantizar intervenciones efectivas. Asimismo, deberían implementarse protocolos individualizados en unidades de Rehabilitación Cardio-Oncológica. Finalmente, resulta imperativo promover el mensaje de evitar la inactividad física en el paciente oncológico.
Introduction

Nowadays in the United States of America, cancer is the second cause of death. It is expected that in the years 2025-2030, cancer will exceed cardiovascular diseases as the principal cause of death. In turn, cardiovascular disease (CVD) is the leading cause of long-term morbidity and death among cancer survivors, after second malignancies.

Cardiotoxicity is defined by the National Cancer Institute as "toxicity that affects the heart." No single, universally defined acceptance is present. Traditionally and thematically cardiotoxicity has been linked with a decline in the Left Ventricular Ejection Fraction (LVEF). According to the European Society of Cardiology, cardiotoxicity leading to heart failure is defined as a decrease in the LVEF >10% points to a value below the lower limit of normality on an echocardiograph, and a relative reduction in global longitudinal strain of >15% from baseline. Heart structure disfunction, haemodynamic flow alterations, hypertension, valvular disease, arrhythmias, thrombotic events and peripheral vascular disease are related with this Cardio-Oncology concept.

By and large, there is a strong connection between cancer treatment-induced cardiotoxicity (CTC) and CVD over treatment and cancer survivorship. For instance, congestive heart failure because of cancer therapy has been linked to a 3.5-fold increased mortality risk compared with idiopathic cardiomyopathy.

Preventing CTC constitutes a crucial endpoint in oncology. Nowadays, an increasing interest in CTC exists in order to encourage individualized treatment planning and the promotion of quality of life. By and large, there is a strong connection between cancer treatment-induced cardiotoxicity (CTC) and CVD over treatment and cancer survivorship. For instance, congestive heart failure because of cancer therapy has been linked to a 3.5-fold increased mortality risk compared with idiopathic cardiomyopathy.

Methods

Search strategy and article selection criteria

This narrative review relied on a comprehensive protocol, covering an ascendant and descendant approach to gather evidence on the effects of physical training to prevent from CTC. Four renowned electronic databases were searched: Medline PubMed, PEDro, Scopus and Web of Science. Also, the list of references of three reference reviews on physical training and cardiotoxicity was reviewed as well as the list of references of all the articles included in this study (descendant approach).

Electronic databases were searched in October 5th 2018. A broadscope and inclusive initial search strategy was carried out with no restrictions in specie, population or age, in order to identify a wide collection of studies on training exercise effects. Thus, search queries included 'cancer' (or 'neoplasms'), 'cardiotoxicity' and 'exercise' as keywords (as well as their related thesaurus terms: for cardiotoxicity, 'cardiac toxicity', or 'heart toxicity'; and for exercise, 'physical training', 'physical activity', 'physical exercise', 'acute exercise', or 'exercise training').

Inclusion criteria for studies were: a) studies analyzing the effects of a physical training-based intervention on human adults samples;
b) studies comprising cancer patients or survivors; c) studies reporting comparative results (i.e., between-group or pre-post test) regarding cardiovascular markers or cardiopulmonary exercise test (e.g., heart rate, cardiopulmonary volume, left ventricular ejection fraction, VO\textsubscript{peak}); d) being an empirical study published in scientific journals; e) article written in English. The exclusion criteria were: a) non-human samples; b) studies combining physical-training treatments and other types of interventions different than usual care (e.g., a surgical intervention, nutritional supplementation, pulmonary/breathing physical therapy protocols, yoga); c) descriptive studies or qualitative studies; d) studies comprising patients without a history of cancer.

**Data extraction and quality assessment**

Articles were screened for a reviewer on an initial review of title, abstract, and keywords. Pre-selected papers were fully read to ratify the selection. An independent peer reviewer confirmed the appropriateness of every paper to be included in this study. Discrepancies on paper selection were resolved by discussion.

Relevant data was extracted using a coding manual. An independent reviewer supervised data entered in the data collection form. Data collected from every study were: a) sample size and composition (i.e., type of cancer participants, cancer stage); b) age range; c) country of recruitment; d) study design; e) VO\textsubscript{peak} and/or cardiac outcome; f) type of exercise training intervention (i.e., aerobic, resistance training, and combined); g) treatment duration and number of sessions; h) intensity of training; i) results of the intervention; j) side effects derived from the interventions; k) and quality of studies based in four criteria described below.

1087 studies were identified through database searching. Studies excluded after screening titles and abstracts (n=944). Titles and abstracts described below. Full-text articles assessed for eligibility: (n=143). Studies included in narrative review (n=33) (Figure 2).

**Cardiovascular training in human**

The intervention by means of physical exercise in humans extrapolates the type of cardiovascular physical exercise, times and intensities used in the research carried out on rodents\textsuperscript{27,31}. In the study of Kirkham et al\textsuperscript{32}, the intensity of the exercise to try to diminish the cardiotoxicity associated with the use of doxorubicin was 70% of the cardiac frequency of reserve of each patient, similar in exercise intervention: Acute (1 single bout) & Intensity seen in rat model\textsuperscript{27}. Haykowsky et al\textsuperscript{33} shows that initiation of trastuzumab is associated with left ventricular cavity dilation and reduced ejection fraction despite aerobic training. Although this important study doesn’t count with a control non-exercise group.

**Resistance training (strength) in human**

Nowadays, there are no exclusive strength interventions in humans trying to reduce CTC in oncological patients (measuring specifically cardiac biomarkers). This could provide new research opportunities.

**Results**

**Intervention programs by means of physical exercise in cancer patients**

Thirty-three studies were included in this review (n=2778 patients). Table 1 displays the main features of these studies. Mean age of participants was 47.1 years, and the most common diagnosis was breast cancer. Sample size of the studies was 84.18 patients on average. Most of studies was based in North America (15 from EEUU and 10 from Canada); 6 from Europe, and 2 from the rest of the world. Regarding study design, interventions during treatment vs. survivors vs. both; Exercise during treatment: 16 studies. Exercise design in survivors: 15. Both: 2 studies.

Most studies were randomized controlled trials (72.72% of articles); 45.45% of them controlled for confounding factors (mainly type of oncology treatment, age and free- cancer time) in randomization or data analysis. On the other hand, most of articles assessed outcomes pre-post tests (60.61% of manuscripts) and 39.39% included follow-up. In terms of type of exercise programs, the bulk of studies used cardiovascular training. Four studies delivered programs integrating cardiovascular and strength modalities (intervention exercise group). Finally, there was a trend towards 3 days/week exercise sessions (45–50 mints. per session): 20 studies. With these 3 weekly exercise sessions, the 150 mints/week, cardiovascular exercise recommendations of American and Australian oncological Societies are fulfilled\textsuperscript{23,20}. 

Quality of studies was assessed by four criteria: a) type of study design (according to, cohort studies or randomized controlled trial show a higher level of evidence, than case- controlled studies or descriptive ones); b) random assignation to interventions; c) confounding control (control of potential confounders); d) repeated measures (whether the study had pre-post tests assessments and follow-up). Two reviewers independently assessed all the studies included in this review. Discrepancies were resolved by discussion.
### Table 1. Main features of studies selected in this review.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Mean age</th>
<th>Cancer site</th>
<th>Severity</th>
<th>Type of intervention</th>
<th>Intervention particularities</th>
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<th>Results</th>
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<tr>
<td>Courneya et al</td>
<td>242</td>
<td>Breast</td>
<td>I-III A</td>
<td>CV vs. ST</td>
<td>Aerobic Exercise Group: 3 days/w; intensity: 60-80% from maximal VO₂ per 15-45 min. Resistance Training: 3 days/w + 9 exercises x 2 sets of 8-12 rep.; intensity: 60-80% (one repetition maximum).</td>
<td>VO₂ Peak.</td>
<td>VO₂ peak increased by 0.2% in aerobic exercise group and decreased by 5% in the resistance training group.</td>
<td></td>
</tr>
<tr>
<td>Courneya et al</td>
<td>122</td>
<td>Lymphoma</td>
<td>All stages</td>
<td>CV</td>
<td>Three days/w with 12 weekly sessions, 15-45 min a session.</td>
<td></td>
<td>VO₂ Peak.</td>
<td></td>
</tr>
<tr>
<td>Courneya et al</td>
<td>301</td>
<td>Breast</td>
<td>I-III C</td>
<td>CV vs. combined</td>
<td>Standard Aerobic Exercise: 3 days/w x 25-30 min; intensity: 55-75% from VO₂ max. High Aerobic Exercise Group: 3 days/w x 50-60 min; intensity: 55-75% from VO₂ peak.  Combined Exercise: 3 days/w of CV training with sessions of 25-30 min (intensity: 55-75% from VO₂ peak) + 2 sets x 10-12 rep (intensity: 60-75% one-repetition maximum).</td>
<td>VO₂ Peak.</td>
<td>VO₂ peak decreased by 12% in the standard aerobic exercise group, 9% in the high aerobic exercise group, and by 13% in the combined exercise group.</td>
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<tr>
<td>Dolan et al</td>
<td>242</td>
<td>Breast</td>
<td>II-III A</td>
<td>CV vs. ST</td>
<td>Aerobic Exercise Group: 3 days/w, with sessions of 15-45 min (intensity: 60-80% from VO₂ peak). Resistance Training Group: 3 days/w x 2 sets of 8-12 rep and 9 exercises (intensity: 60-70% of one-repetition maximum).</td>
<td>VO₂ Peak.</td>
<td>The resistance training (and the usual care group) showed increase in VO₂ peak. Both exercise groups showed moderate correlation between VO₂ peak change and hemoglobin.</td>
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<td>Haykowsky et al</td>
<td>17</td>
<td>Breast</td>
<td>All stages</td>
<td>CV</td>
<td>Three days/w x 16 weeks x 30-60 min (intensity: 60-90% from VO₂ peak).</td>
<td>VO₂ Peak.</td>
<td>VO₂ peak positively correlated with exercise adherence. Intervention led to resting BP volume increase and ejection function decrease.</td>
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<tr>
<td>Hornsby et al</td>
<td>20</td>
<td>Breast</td>
<td>IIB-III C</td>
<td>CV</td>
<td>Three days/w and sessions of 15-45 min (intensity: 60-100% from VO₂ peak). The program lasted 12 weeks (last two with higher intensity: 100% from VO₂ peak).</td>
<td>VO₂ Peak.</td>
<td>VO₂ peak increased by 13% in the exercise group. No significant between-group differences in terms of HR, BP and LVEF.</td>
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<tr>
<td>Jones et al</td>
<td>20</td>
<td>Breast</td>
<td>II-III C</td>
<td>CV</td>
<td>Aerobic Exercise Group: 3 days/w x 12 weeks x 30-45 min (intensity: 60-100 from VO₂ peak).</td>
<td>VO₂ Peak.</td>
<td>VO₂ peak increased by 13% in the exercise group. Higher levels of circulating progenitor cell in the exercise group in comparison to controls, as well as greater brachial dilation.</td>
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(Continued)
<table>
<thead>
<tr>
<th>Study</th>
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<td>Kim et al</td>
<td>41</td>
<td>49.8</td>
<td>Breast</td>
<td>I-III</td>
<td>CV</td>
<td>Three days/w and sessions of 30 min (intensity: 60-70% from VO\textsubscript{2} peak or HR reserve).</td>
<td>VO\textsubscript{2}, Peak. HR. BP.</td>
<td>The exercise group showed significant increases in maximum systolic BP volume and VO\textsubscript{2} peak, as well as decreases in resting HR and resting systolic BP.</td>
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<td>Kirkham et al</td>
<td>24</td>
<td>50.5</td>
<td>Breast</td>
<td>I-III</td>
<td>CV</td>
<td>A single session of 45-min treadmill exercise (intensity: 70% from HR reserve).</td>
<td>Cardiac biomarkers (NT-proBNP, cTnT). HR. Systemic vascular resistance. LV volume and LVEF.</td>
<td>VO\textsubscript{2}, peak increased by 15% in the exercise group. Higher levels of cardiac biomarkers in the exercise group. LVEF increased by 3% after intervention in the exercise group.</td>
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<tr>
<td>Kolden et al</td>
<td>40</td>
<td>55.3</td>
<td>Breast</td>
<td>I-III</td>
<td>Combined + stretching</td>
<td>Three days/w with 20-min aerobic exercise (intensity: 40-70 from VO\textsubscript{2} peak) + 20-min strength training (not reported intensity) + Stretching.</td>
<td>VO\textsubscript{2}, Peak. Resting HR and BP.</td>
<td>VO\textsubscript{2}, Peak increased at post-intervention assessment and follow-up. Resting systolic BP across assessment points.</td>
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<td>Ligibel et al</td>
<td>41</td>
<td>47</td>
<td>Breast</td>
<td>I-III</td>
<td>CV</td>
<td>An aerobic exercise program with sessions of 150 min/w.</td>
<td>VO\textsubscript{2}, Peak.</td>
<td>VO\textsubscript{2}, peak increased by 4% in the exercise group.</td>
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<td>MacVicar</td>
<td>45</td>
<td>45.1</td>
<td>Breast</td>
<td>II</td>
<td>CV</td>
<td>Usual Care + Stretching + cardiovascular training (3 sessions/w; intensity: 60-85% from resting HR).</td>
<td>VO\textsubscript{2}, Peak.</td>
<td>IG increased 40% of functional capacity and maximum workload.</td>
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<td>Scott et al</td>
<td>65</td>
<td>54</td>
<td>Breast</td>
<td>IV</td>
<td>CV vs. Others</td>
<td>Aerobic Exercise Group: 3 days/w x 20-45 min (intensity: 55-80 from VO\textsubscript{2} peak). Stretching Group: 3 days/w x 20-45 min (12-20 positions).</td>
<td>VO\textsubscript{2}, Peak. BP.</td>
<td>No significant differences between groups.</td>
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<td>Segal et al</td>
<td>123</td>
<td>50.9</td>
<td>Breast</td>
<td>I-II</td>
<td>CV</td>
<td>Supervised Group: 3 days/w + 2 days/w at home during 26 weeks. Home Based Group: 5 days/w of exercise at home (26 weeks).</td>
<td>VO\textsubscript{2}, Peak.</td>
<td>VO\textsubscript{2}, peak increased by 3.5% in supervised exercise group and 2.4% in the home-based group.</td>
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<tr>
<td>Segal et al</td>
<td>121</td>
<td>66.3</td>
<td>Prostate</td>
<td>All stages</td>
<td>CV vs. ST</td>
<td>Aerobic Exercise Group: 3 days/w x 15-45 min sessions during 24 weeks (intensity: 50-75% from VO\textsubscript{2} peak). Resistance Training: 3 days/w with 10 exercises of 8-12 rep.; intensity: 60-70% from VO\textsubscript{2} peak (one repetition maximum).</td>
<td>VO\textsubscript{2}, Peak.</td>
<td>VO\textsubscript{2}, peak increased by 0.1% in the aerobic exercise group and 0.5% in the resistance training group.</td>
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<td>Van Waart et al</td>
<td>230</td>
<td>50.7</td>
<td>Breast &amp; colon</td>
<td>II-III</td>
<td>CV vs. combined</td>
<td>Onco Move Group (CV program): 5 days/w x 30 min/day; intensity: BORG Scale of 12-14. On Track Group (combined program): 3 days/w x 30 min (intensity: 50-80% based on Steep Ramp Test) + 2 days/w x 20 min x 2 sets x 8 rep. x 80% of one-repetition maximum.</td>
<td>VO\textsubscript{2}, Peak.</td>
<td>VO\textsubscript{2}, peak decreased by 18% in the Onco Move group and by 12% in the On Track group.</td>
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<td>Vincent et al</td>
<td>34</td>
<td>49</td>
<td>Breast</td>
<td>I-III</td>
<td>CV</td>
<td>Home-based walking aerobic exercise (3 days/w of 30-40 min sessions, with 50-60% from HR max intensity).</td>
<td>VO\textsubscript{2}, Peak. Resting HR. Resting BP.</td>
<td>VO\textsubscript{2}, peak increased by 11% in the exercise group. No significant between-group differences in terms of HR and BP.</td>
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<tr>
<td>Study</td>
<td>Sample size</td>
<td>Mean age</td>
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<td>Survivor samples</td>
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<tr>
<td>Adams et al</td>
<td>63</td>
<td>43.7</td>
<td>Testicular</td>
<td>Not reported</td>
<td>Cardiovascular</td>
<td>Supervised treadmill program consisted of 3 days/w x 12 weeks, 35-min sessions and interval training (Ventilatory Threshold +4x4 min and intensity 75-95% from VO(_2) peak).</td>
<td>VO(_2) Peak. HR. BP. Cardiovascular disease risk. Carotid artery morphology. Brachial artery flow-mediated dilation.</td>
<td>VO(_2) peak increased by 11% in the exercise group. The exercise group showed higher carotid distensibility and brachial artery diameter, and lower carotid intima-media thickness.</td>
</tr>
<tr>
<td>Brdareski et al</td>
<td>18</td>
<td>50.5</td>
<td>Breast</td>
<td>I-IIIA</td>
<td>Cardiovascular</td>
<td>Group 1: Two days/w x 3 weeks and 15-min sessions (intensity: 45-65% VO(_2) max). Group 2: Two days/w x 3 weeks and 15-min sessions (intensity: Borg Scale scores between 4-6).</td>
<td>VO(_2) Peak.</td>
<td>VO(_2) peak increased by 11% in the Group 1 and 18% in the Group 2.</td>
</tr>
<tr>
<td>Courneya et al</td>
<td>53</td>
<td>59</td>
<td>Breast</td>
<td>All stages</td>
<td>Cardiovascular</td>
<td>Three days/w x 15-35 min (intensity: 70-75% from VO(_2) peak).</td>
<td>VO(_2) Peak.</td>
<td>VO(_2) peak increased by 15% in the exercise group.</td>
</tr>
<tr>
<td>Herrero et al</td>
<td>16</td>
<td>50.5</td>
<td>Breast</td>
<td>I-II</td>
<td>Combined</td>
<td>Aerobic training: 3 days/w (intensity: 70-80% from HR max). Resistance Training: 3 days/w x 1-3 sets of 11 exercises and 8-15 rep. (intensity: 8-15 one-repetition maximum).</td>
<td>VO(_2) Peak.</td>
<td>VO(_2) peak increased by 8% in the exercise group.</td>
</tr>
<tr>
<td>Herrero et al</td>
<td>11</td>
<td>47</td>
<td>Breast</td>
<td>I-II</td>
<td>Combined</td>
<td>Training period: 3 days/w during eight w, 90-min sessions. After the intervention, participants were instructed to return following their sedentary lifestyle.</td>
<td>VO(_2) Peak.</td>
<td>VO(_2) peak decreased significantly after returning to sedentary lifestyle routines.</td>
</tr>
<tr>
<td>Hsieh et al</td>
<td>96</td>
<td>57.9</td>
<td>Breast</td>
<td>All</td>
<td>Combined</td>
<td>A program consisted of 2-3 weekly sessions of 60 min (intensity: 45-75% from HR reserve; not specified for resistance training).</td>
<td>VO(_2) Peak. HR. BP.</td>
<td>The exercise group showed increases in VO(_2) volume (over 16%) and resting HR.</td>
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<td>Hutnick et al</td>
<td>49</td>
<td>50.4</td>
<td>Breast</td>
<td>All</td>
<td>Combined</td>
<td>Three days/w of 40-90 min. sessions. Aerobic Exercise: 10-20 min with intensity 60-70% from functioning capacity. Resistance training: Four upper &amp; lower exercise x 1-3 sets of 8-12 rep.</td>
<td>HR peak.</td>
<td>HR peak increased in the exercise group from the 3-month follow-up after the intervention.</td>
</tr>
<tr>
<td>Jones et al</td>
<td>90</td>
<td>66</td>
<td>All (Cancer patients with heart failure)</td>
<td>II-IV</td>
<td>Cardiovascular</td>
<td>A 3-Month program comprising supervised Exercise + home Sessions until 12 months. 3 days/w x 20-45 min (intensity: 60-70% from HR reserve).</td>
<td>VO(_2) Peak. Cardiovascular risk profile.</td>
<td>VO(_2) peak increased by 9% in the exercise group. No between-group differences in cardiovascular risk profile.</td>
</tr>
<tr>
<td>Jones et al</td>
<td>50</td>
<td>Not reported</td>
<td>Prostate</td>
<td>I-II</td>
<td>Cardiovascular</td>
<td>Aerobic walking Exercise of 5 days/w x 30-45 min, a session (intensity: 55-100 from VO(_2) peak).</td>
<td>VO(_2) Peak. Brachial artery flow mediated dilation.</td>
<td>VO(_2) peak increased by 9% in the exercise group. Higher brachial arterial diameter after the intervention only in the exercise group.</td>
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<tr>
<td>Musanti et al</td>
<td>42</td>
<td>50.5</td>
<td>Breast</td>
<td>I-IIIB</td>
<td>CV vs. ST vs. Others</td>
<td>Aerobic exercise Group: 3 days/w (intensity: 40-85% from HR reserve), Resistance Training Group: 3 days/w x 1 set of 10-12 rep (intensity: 3-8 from one-repetition maximum), Combined Exercise Group: 4-5 days/w aerobic training + 2 days/w resistance training.</td>
<td>VO₂ Peak</td>
<td>No significant between-group differences reported.</td>
</tr>
<tr>
<td>Pinto et al</td>
<td>46</td>
<td>57.3</td>
<td>Colorectal</td>
<td>I-III</td>
<td>CV</td>
<td>12-week home-based physical activity counselling (2-5 days/w x 10-30 min, with intensity 64-76% from maximal HR).</td>
<td>VO₂ peak</td>
<td>VO₂ peak: Control Group =Increased 15%; Exercise Group =Increased 32%</td>
</tr>
<tr>
<td>Rahnama et al</td>
<td>29</td>
<td>Range: 50-65 years old</td>
<td>Breast</td>
<td>I-IIIB</td>
<td>Combined</td>
<td>Aerobic Exercise: 2 days/w x 25-45 min sessions (intensity: 45-65% from HR maximum) + Resistance training: 2 days/w consisting of 3 sets x 10-14 rep. x 9 exercises.</td>
<td>VO₂ Peak, Resting HR, BP</td>
<td>VO₂ peak increased by 15% in the exercise group. The exercise group showed significant decrease in resting HR and resting BP after intervention.</td>
</tr>
<tr>
<td>Rogers et al</td>
<td>41</td>
<td>53</td>
<td>Breast</td>
<td>I-IIIA</td>
<td>CV</td>
<td>Combined individual and collective group aerobic exercise group.</td>
<td>VO₂ Peak</td>
<td>No significant between-group differences reported.</td>
</tr>
<tr>
<td>Rogers et al</td>
<td>222</td>
<td>54.4</td>
<td>Ductal Carcinoma &amp; breast</td>
<td>I-IIIA</td>
<td>CV</td>
<td>Twelve sessions of supervised Exercise + 6 group discussion and individual Sessions. 3-5 days/w x 15-50 min.</td>
<td>VO₂ Peak</td>
<td>VO₂ peak increased by 12% in the exercise group.</td>
</tr>
<tr>
<td>Schneider et al</td>
<td>113</td>
<td>55.9</td>
<td>Breast</td>
<td>Not reported</td>
<td>Combined</td>
<td>Combined individual aerobic + resistance exercise: 2-3 days/w of 60-min sessions. Aerobic exercise lasted 40 min (intensity: 40-75% from HR reserve), Resistance training lasted 10 min (intensity not specified).</td>
<td>VO₂ Peak, BP Resting HR</td>
<td>BP decreased while exercise intervention was delivered. Resting HR and BP decreased at post-intervention. Also, VO₂ peak increased by 13% in this condition.</td>
</tr>
<tr>
<td>Thorsen et al</td>
<td>111</td>
<td>39.1</td>
<td>Lymphoma, testicular, breast and other gynecologic Cancers</td>
<td>All stages</td>
<td>CV</td>
<td>Home-based program: 2 days/w x 30 min (13-15 based on BORG Scale).</td>
<td>VO₂ Peak</td>
<td>VO₂ peak: Control Group =Increased 3.1 ml/kg/min. Home Exercise Group =Increased 6.4 ml/kg/min</td>
</tr>
</tbody>
</table>

Note: The 33 bibliographic references included in Table 1 can be found online in Annex 1.

CV: cardiovascular training; ST: Strength; HR: heart rate; w: weeks; rep.: repetitions; VO₂: Volume of oxygen consumed; BP: Blood pressure; LV: Left ventricle; LVEF: left ventricular ejection function; NT-proBNP: B-type natriuretic peptide; cTnT: Cardiac Troponin T.

Discussion

Our narrative review aimed to fill the research gap on how physical exercise may contribute to reduce cardiotoxicities associated with oncological treatments (chemotherapy, radiotherapy, hormonotherapy and / or immunotherapy).

Current diagnostic techniques are important to keep in mind when talking about cardiotoxicity: Diagnostic imaging and Biomarkers in cardio-oncology. Traditionally, left ventricular ejection fraction (LVEF) has been used (i.e., a 2D echocardiogram) to quantify cardiotoxicity (Figure 3). However, a cardiac injury may exist underlying an apparently ‘normal’ heart’s ejection (i.e., without a decrease in the LVEF), as some authors have demonstrated significant false-positive rates of LVEF-based tools. Cardiac Magnetic Resonance Imaging is considered as the gold standard for the assessment of systolic and diastolic cardiac function and allows for direct imaging of the myocardium (Figure 4). Lately, cardiac biomarkers (e.g., troponin I, natriuretic peptide B-type) have emerged as a promising alternative to study cardiotoxicity.
However, inconsistent evidence and limited predictive value have found so far. More recently, Galán-Arriola et al. have identified by serial multiparametric cardiac Magnetic Resonance, intracardimyoocyte edema in T2 mapping as the earliest marker of anthracycline cardiotoxicity, in the absence of T1 mapping, extracellular volume or left ventricl motion defects.

It seems to be that key elements behind any carcinogenic process is the dysregulation of signs controlling the proliferation of cellular division and inflammation. By means of the regulation of certain proteins and hormonal levels in the bloodstream, physical exercise might prevent some chemical signs associated with cancer.

Reviewing the available evidence, it becomes evident that the etiology of cardiotoxicity is multifactorial. Nevertheless, it is clear that in the scientific literature, the following mechanisms related to molecular and cellular biology are repeated:

- Disorder and dysfunction of the Ryanodine receptors (RyR).
- Disorder and dysfunction, both at a structural and contractile level, of the Myosin heavy chain (MHC).
- Disorder and Dysfunction in the Tyrosine Kinase protein.
- Excess of production of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS).
- Deficiency and mitochondrial dysfunction.

Figure 3. 2D Echocardiography showing aberrant movement and hypokinesia of inferior wall and septum in a patient diagnosed of dilated myocardiopathy as a consequence of doxorubicin, trastuzumab and radiotherapy treatment for breast cancer.

Figure 4. Cardiac Magnetic Resonance Imaging to evaluate function, morphology and viability.

Left ventricle lightly dilated and global hypokinesis with LVEF 31%, in a patient diagnosed with Hodgkin lymphoma 30 years before treated with radiotherapy.
The improvement of the vascularization tissue seems to improve not only the tissue oxygenation but also the action of the antitumor treatments. In the case of treatment with anthracyclines, physical exercise lightens these products in order to not be stored in the organism and generate toxic effects in the cardiovascular system.\(^{44,45}\)

It is important to emphasize the role accumulation of doxorubicin in muscular tissues of rats. This accumulation would explain the dysfunctions associated not only with the cardiovascular system, but also with the skeletal muscle system. Research literature found a reduction in the tumor size linked to exercise. Through physical exercise, the bioavailability of anthracyclines may improve, as well as the efficiency of the drug in its antitumor aspect.

Moreover, Pedersen et al.\(^{46}\), demonstrated the immunological protective effect of exercise in mice. The interaction between epinephrine, muscular interleukin 6 and Natural Killer cells generated marked reductions in tumor incidence, growth and metastasis.

Exercise improves the vessel reactivity before the treatment of anthracyclines. In the group where physical exercise was carried out, vasoreactivity obtained values significantly better than the sedentary group.

Exercise interventions have been obtained results of improvement in cardiac function and cardiac damage markers during treatments with anthracyclines\(^{38,39}\). Perhaps with the knowledge that is currently available, said cardiac dysfunction may have been reduced or prevented by physical exercise before or during anthracycline treatments.

There are no exclusive strength interventions in humans trying to reduce CTC in oncological patients. The fact to do a special mention of the strength training in this article, is related with the tumoral disease and with the consequences with respect to the organ we have focused: the heart. In cardiotoxicity with oncological origin 2 types of patients could be found from a medical point of view: one will be seen from the oncology focus, and the other from the pathology and functionality of cardiology.

The studies by Bredahl et al.\(^{23}\) and Pfannenstiel et al.\(^{24}\) focused on interventions using resistance exercise on Sprague-Dawley rats which cardiotoxicity were induced by doxorubicin. The intervention through physical exercise is done prior to the administration of doxorubicin. The resistance exercise allows to maintain levels of strength and prevent muscle mass loss induced by doxorubicin; one of the most common side effects in chemotherapy. Pfannenstiel et al.\(^{24}\), shows that this muscle-protective effect could not only be quantified with respect to a greater muscle mass, but also in a lower mortality rate: 13% mortality in the strength group vs 27% sedentary group. The strength group also had a cardioprotective effect with respect to heart mass and function.

Although Cardiac Rehabilitation Units (CRU) are doing an excellent work, we based our proposal of strength training in Cardio-Oncology on 2 aspects:

- Defining Repetition Maximum (RM) as the maximal weight that can be lifted once with correct lifting technique\(^{48}\). It is also considered the gold standard for assessing muscle strength in non-laboratory situations\(^{39}\). There are some examples in the literature in patients with heart disease in which the strength training was performed at intensities of 80-90% of 1 Repetition Maximum (1RM), in coronary patients\(^{38,39}\), intensities up to 60% 1RM in bilateral work (both members), and up to 80% 1RM in unilateral work, in patients with heart failure with an ejection fractions of 20% according to NYHA Classification (New York Heart Association)\(^{53}\). This could be extrapolated to oncological patients with risk of CTC due to the treatments. The World Health Organization\(^{13}\) included specific strength work in its guidelines on Global Recommendations on Physical Activity for Health.

- Traditionally, cardiovascular training has been considered as the most protective physical exercise applied in medicine. In the 80s of the twentieth century, exercise-based interventions in oncological patients have already been used\(^{41}\). Later on, the first guide that linked physical exercise and oncology was developed\(^{41}\). More recently, the experts in the delivery of exercise-based interventions in cancer patients recommend combined interventions, comprising cardiovascular and strength training\(^{50}\).

Strength training components may yield very beneficial effects in cancer patients\(^{56,57}\). Improvements in cardiovascular function, increases in VO\textsubscript{peak}, a decrease in fatigue levels, increases in muscular strength and density of osseous mass, improvement in the quality of life, prevention of sarcopenia and dynapenia, and a decrease in the percentages of fat mass.

From early studies in exercise oncology until today, many advances linked to the clinical exercise physiology have been made. It has even been discovered that the skeletal muscle is an endocrine, exocrine and paracrine organ\(^{19}\), and produced proteins (including different cytokines and peptides) are known as myokines.

At present, it is starting to be considered that physical exercise might generate, in each training session, peaks of chemical components, which could be used not only as co-adjuvant anticarcinogenic treatment\(^{59}\), but also for 26 different chronic diseases\(^{1}\). We propose combined exercise interventions to reduce the risks of Cardiotoxicity in cancer patients as co-adjuvant treatment: Cardiovascular Training in combination with Strength Training. Recently, the AHA has confirmed this combined tailored exercise in his Cardio-Oncology Rehabilitation Statement\(^{11}\).

**Conclusions**

Cancer treatments cause dysfunction in muscular tissue (cardiac, skeletal and smooth muscle) and loss of muscular strength. Physical exercise can offset the side effects of cancer treatments. There are biological reasons (cellular, molecular and biochemical release) that explain the cardiovascular and muscular protective effect of exercise in Exercise Oncology. It is advisable to introduce intervention programs with personalized physical exercise in cancer patients for the protective effects that it generates. Training interventions should comprise cardiovascular and muscular strength exercise with personalized frequencies, intensities...
and specific durations for every patient. It is necessary to avoid physical inactivity in patients with cancer.

References

Tailored exercise as a protective tool in cardio-oncology rehabilitation: a narrative review

Kim CJ, Kang DH, Smith BA, Landers KA. Cardiopulmonary responses and adherence to
Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS. Randomized controlled
Pinto BM, Papandonatos GD, Goldstein MG, Marcus BH, Farrell N. Home-based physical

Annex 1. List of 33 studies references included in the Narrative Review.


• Kielholm AA, Shave RE, Bland KA, Boward JM, Evens ND, Gelmon KA, et al. Protective effects of acute exercise prior to docetaxol on cardiac function of breast cancer patients: A proof of concept RCT. Int J Cardiol. 2017;243:263-270.


