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, personalized 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:
Cardiovascular disease. Cancer. Cardiotoxicity. Exercise & Cardio-Oncology Rehabilitation.

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.

Palabras clave:
Patología cardiovascular. Cáncer. Cardiotoxicidad. Ejercicio & Rehabilitación Cardio-Oncológica.

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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[1]. In turn, cardiovascular disease (CVD) is the leading cause of long-term morbidity and death among cancer survivors, after second malignancies[2].

Cardiotoxicity is defined by the National Cancer Institute as "toxicity that affects the heart". No single, universally definition is accepted at 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[3]. 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[4,5]. For instance, congestive heart failure because of cancer therapy has been linked to a 3.5-fold increased mortality risk compared with idiopathic cardiomyopathy[6].

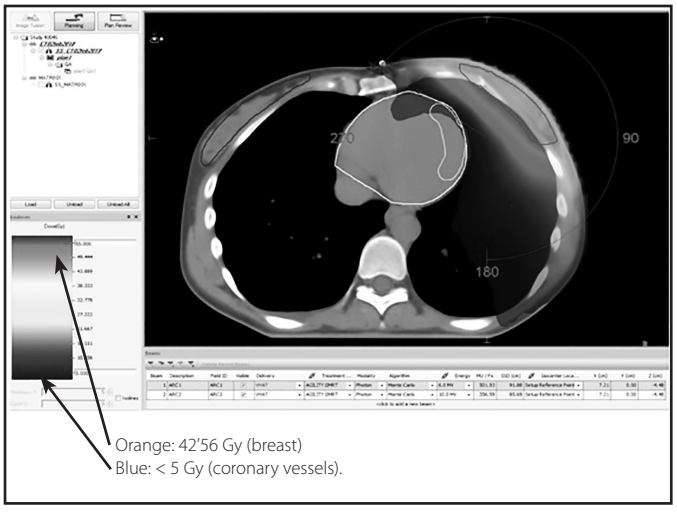
Preventing CTC constitutes a crucial endpoint in oncology. Nowadays, an increasing interest in CTC exists in order to encourage individualized treatment planning and the promotion of quality of life across cancer treatment and survivorship. Thus, several studies have provided new insight on the relationship between chemotherapy agents[7,8], adjuvant endocrine therapy[8], and monoclonal antibodies and CTC[8]. Likewise, some studies have stress the association of radiotherapy exposure (Figure 1) and CTC[7-10].

Based on experience in the area of cardiac rehabilitation and exercise oncology units, the potential use of physical exercise as a co-adjuvant treatment has been endorsed[11]. Mounting evidence has proved that physical exercise improves cardiovascular function and facilitates cardiac rehabilitation[12,13]. The American Association of Clinical Oncology (ASCO) has recently highlighted the role of physical exercise as an essential component of cancer survivor care programs[14]. In this line, the American Heart Association (AHA) suggests the implementation of tailored exercise for Cardio-Oncology Rehabilitation[15].

Exercise training may protect from cardiotoxicity on a molecular basis. In this sense, exercise promotes effective regulation of calcium channel in ryanodine receptors, which are involved in heart contractile function[16]. Moreover, physical exercise may contribute antioxidant agents to be produced and mitochondrial function be improved[17-19]. From a patient point of view, physical exercise has significant benefits to tackle CTC. Several modalities of exercise training are present in rehabilitation contexts, two major types of training in this field are: cardiovascular and resistance/strength training. The bulk of studies have concentrated on cardiovascular programs and their effectiveness to prevent CTC[20-22]. Some studies have reported the benefits of resistance physical training on cardiovascular and musculoskeletal systems and its potential protective effects, specifically in Sprague- Dawley rats which were induced CTC through doxorubicin[23,24]. Little is known about the effects of these interventions in cancer patients and survivors. Moreover, integrated programs (i.e., programs combining cardiovascular and resistance components) have been scarcely studied.

This narrative review aimed to examine the scientific literature in order to explore and gather studies focused on physical training applications as adjuvant interventions to tackle CTC. Moreover, we intended to describe the main features of interventions that have been proven effective to deal with CTC (e.g., treatment duration, training components, outcomes to consider). Finally, we aimed at providing recommendations and some guidelines to design physical training interventions in cancer settings, considering their cardioprotective benefits.

Figure 1. Left Breast Cancer Radiotherapy with Volume Modulated Arc (VMAT) and 6-10 MV.



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[4,20,21] 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 broad-scope 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_2peak); 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.

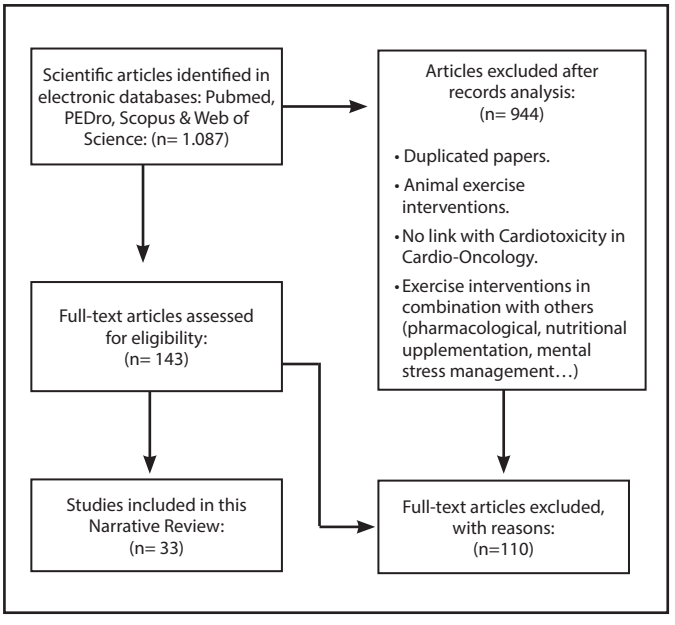
Data extraction and quality assessment

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_2peak 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 identified (n=143). Studies included in narrative review (n=33) (Figure 2).

Figure 2. Flow Diagram.



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.

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[25,26].

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[27-31].

In the study of Kirkham *et al*[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[30].

Haykowsky *et al*[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.

Table 1. Main features of studies selected in this review.

Study	Sample size	Mean age	Cancer site	Severity	Type of intervention	Intervention particularities	Outcome	Results
Patient samples								
Courneya *et al*	242	49.2	Breast	I-IIIA	CV vs. ST	Aerobic Exercise Group: 3 days/w; intensity: 60-80% from maximal VO_2 per 15-45 min. Resistance Training: 3days/w + 9 exercises x 2 sets of 8-12 rep.; intensity: 60-80% (one repetition maximum).	VO_2 Peak.	VO_2 peak increased by 0.2% in aerobic exercise group and decreased by 5% in the resistance training group.
Courneya *et al*	122	53.2	Lymphoma	All stages	CV	Three days/w with 12 weekly sessions, 15-45 min a session.	VO_2 Peak	VO_2 peak increased by 17% in the exercise group.
Courneya *et al*	301	50	Breast	I-IIIC	CV vs. combined	Standard Aerobic Exercise: 3 days/w x 25-30 min; intensity: 55-75% from VO_2 max. High Aerobic Exercise Group: 3 days/w x 50-60 min; intensity: 55-75% from VO_2 peak. Combined Exercise: 3 days/w of CV training with sessions of 25-30 min (intensity: 55-75% from VO_2 peak) + 2 sets x 10-12 rep (intensity: 60-75% one-repetition maximum).	VO_2 Peak	VO_2 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.
Dolan *et al*	242	49.2	Breast	II-IIIA	CV vs. ST	Aerobic Exercise Group: 3 days/w, with sessions of 15-45 min (intensity: 60-80% from VO_2 peak). Resistance Training Group: 3 days/w x 2 sets of 8-12 rep and 9 exercises (intensity: 60-70% of one-repetition maximum).	VO_2 Peak.	The resistance training (and the usual care group) showed increase in VO_2 peak. Both exercise groups showed moderate correlation between VO_2 peak change and hemoglobin.
Haykowsky *et al*	17	53	Breast with HER2	All stages	CV	Three days/w x 16 weeks x 30-60 min (intensity: 60-90% from VO_2 peak).	VO_2 Peak. LV volume and LVEF. HR. BP.	VO_2 peak positively correlated with exercise adherence. Intervention led to resting BP volume increase and ejection function decrease.
Hornsby *et al*	20	48.5	Breast	IIB-IIIC	CV	Three days/w and sessions of 15-45 min (intensity: 60-100% from VO_2 peak). The program lasted 12 weeks (last two with higher intensity: 100% from VO_2 peak).	VO_2 Peak. HR. BP. LVEF.	VO_2 peak increased by 13% in the exercise group. No significant between-group differences in terms of HR, BP and LVEF.
Jones *et al*	20	48.5	Breast	II-IIIC	CV	Aerobic Exercise Group: 3 days/w x 12 weeks x 30-45 min (intensity: 60-100 from VO_2 peak).	VO_2 Peak. Brachial artery flow-mediated dilation. Circulating endothelial progenitor cell count (VEGFR-2, CD-133/VEGFR-2, $ALDH^{br}$).	VO_2 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.

(Continued)

Study	Sample size	Mean age	Cancer site	Severity	Type of intervention	Intervention particularities	Outcome	Results
Kim *et al*	41	49.8	Breast	I-III	CV	Three days/w and sessions of 30 min (intensity: 60-70% from VO_2 peak or HR reserve).	VO_2 Peak. HR. BP.	The exercise group showed significant increases in maximum systolic BP volume and VO_2 peak, as well as decreses in resting HR and resting systolic BP.
Kirkham *et al*	24	50.5	Breast	I-III	CV	A single session of 45-min treadmill exercise (intensity: 70% from HR reserve).	Cardiac biomarkers (NT-proB-NP, cTnT). HR. Systemic vascular resistance. LV volume and LVEF.	VO_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.
Kolden *et al*	40	55.3	Breast	I-III	Combined + stretching	Three days/w with 20-min aerobic exercise (intensity: 40-70 from VO_2 peak) + 20-min strength training (not reported intensity) + Stretching.	VO_2 Peak. Resting HR and BP.	VO_2 Peak increased at post-intervention assessment and follow-up. Resting systolic BP across assessment points.
Ligibel *et al*	41	47	Breast	I-III	CV	An aerobic exercise program with sessions of 150 min/w.	VO_2 Peak.	VO_2 peak increased by 4% in the exercise group.
MacVicar	45	45.1	Breast	II	CV	Usual Care + Stretching + cardiovascular training (3sessions/w; intensity: 60-85% from resting HR).	VO_2 Peak	IG increased 40% of functional capacity and maximum workload.
Scott *et al*	65	54	Breast	IV (metastatic)	CV vs. Others	Aerobic Exercise Group: 3 days/w x 20-45 min (intensity: 55-80 from VO_2 peak). Stretching Group: 3 days/w x 20-45 min (12-20 positions).	VO_2 Peak. BP.	No significant differences between groups.
Segal *et al*	123	50.9	Breast	I-II	CV	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).	VO_2 Peak.	VO_2 peak increased by 3.5% in supervised exercise group and 2.4% in the home-based group.
Segal *et al*	121	66.3	Prostate	All stages	CV vs. ST	Aerobic Exercise Group: 3 days/w x 15-45 min sessions during 24 weeks (intensity: 50-75% from VO_2 peak). Resistance Training: 3 days/w with 10 exercises of 8-12 rep.; intensity: 60-70% from VO_2 peak (one repetition maximum).	VO_2 Peak	VO_2 peak increased by 0.1% in the aerobic exercise group and 0.5% in the resistance training group.
Van Waart *et al*	230	50.7	Breast & colon	II-III	CV vs. combined	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.	VO_2 Peak	VO_2 peak decreased by 18% in the Onco Move group and by 12% in the On Track group.
Vincent *et al*	34	49	Breast	I-III	CV	Home-based walking aerobic exercise (3 days/w of 30-40 min sessions, with 50-60% from HR max intensity).	VO_2 Peak. Resting HR. Resting BP	VO_2 peak increased by 11% in the exercise group. No significant between-group differences in terms of HR and BP.

(Continued)

Study	Sample size	Mean age	Cancer site	Severity	Type of intervention	Intervention particularities	Outcome	Results
Survivor samples								
Adams *et al*	63	43.7	Testicular	Not reported	CV	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).	VO_2 Peak. HR. BP. Cardiovascular disease risk. Carotid arteria morphology. Brachial arteria flow-mediated dilation	VO_2 peak increased by 11% in the exercise group. The exercise group showed higher carotid distensibility and brachial arteria diameter, and lower carotid intima-media thickness.
Brdareski *et al*	18	50.5	Breast	I-IIIA	CV	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).	VO_2 Peak.	VO_2 peak increased by 11% in the Group 1 and 18% in the Group 2.
Courneya *et al*	53	59	Breast	All stages	CV	Three days/w x 15-35 min (intensity: 70-75% from VO_2 peak).	VO_2 Peak.	VO_2 peak increased by 15% in the exercise group.
Herrero *et al*	16	50.5	Breast	I-II	Combined	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).	VO_2 Peak.	VO_2 peak increased by 8% in the exercise group.
Herrero *et al*	11	47	Breast	I-II	Combined	Training period: 3 days/w during eight w, 90-min sessions. After the intervention, participants were instructed to return following their sedentary lifestyle.	VO_2 Peak.	VO_2 peak decreased significantly after returning to sedentary lifestyle routines.
Hsieh *et al*	96	57.9	Breast	All	Combined	A program consisted of 2-3 weekly sessions of 60 min (intensity: 45-75% from HR reserve; not specified for resistance training).	VO_2 Peak. HR. BP.	The exercise group showed increases in VO_2 volume (over 16%) and resting HR.
Hutnick *et al*	49	50.4	Breast	All	Combined	Three days/w of 40-90 min. sessions. Aerobic Exercise: 10-20 min with intensity 60-70% from functioning capacity. Resistance training: Four upper & lower exercise x 1-3 sets of 8-12 rep.	HR peak.	HR peak increased in the exercise group from the 3-month follow-up after the intervention.
Jones *et al*	90	66	All (Cancer patients with heart failure)	II-IV	CV	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).	VO_2 Peak. Cardiovascular risk profile.	VO_2 peak increased by 9% in the exercise group. No between-group differences in cardiovascular risk profile.
Jones *et al*	50	Not reported	Prostate	I-II	CV	Aerobic walking Exercise of 5 days/w x 30-45 min, a session (intensity: 55-100 from VO_2 peak).	VO_2 Peak. Brachial artery flow mediated dilation.	VO_2 peak increased by 9% in the exercise group. Higher brachial arterial diameter after the intervention only in the exercise group.

(Continued)

Study	Sample size	Mean age	Cancer site	Severity	Type of intervention	Intervention particularities	Outcome	Results
Musanti *et al*	42	50.5	Breast	I-IIIB	CV vs. ST vs. Combined vs. Others	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.	VO_2 Peak.	No significant between-group differences reported.
Pinto *et al*	46	57.3	Colorectal	I-III	CV	12-week home-based physical activity counselling (2-5 days/w x 10-30 min, with intensity 64-76% from maximal HR).	VO_2 peak.	VO_2 peak: Conrol Group =Increased 15%. Exercise Group =Increased 32%
Rahnama *et al*	29	Range: 50-65 years old	Breast	I-IIIB	Combined	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.	VO_2 Peak. Resting HR. BP.	VO_2 peak increased by 15% in the exercise group. The exercise group showed significant decrease in resting HR and resting BP after intervention.
Rogers *et al*	41	53	Breast	I-IIIA	CV	Combined individual and collective group aerobic exercise group.	VO_2 Peak.	No significant between-group differences reported.
Rogers *et al*	222	54.4	Ductal Carcinoma & breast	I-IIIA	CV	Twelve sessions of supervised Exercise + 6 group discussion and individual Sessions. 3-5 days/w x 15-50 min.	VO_2 Peak.	VO_2 peak increased by 12% in the exercise group.
Schneider *et al*	113	55.9	Breast	Not reported	Combined	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).	VO_2 Peak. BP. Resting HR.	BP decreased while exercise intervention was delivered. Resting HR and BP decreased at post-intervention. Also, V02 peak increased by 13% in this condition.
Thorsen *et al*	111	39.1	Lymphoma, testicular, breast and other gynecologic Cancers	All stages	CV	Home-based program: 2 days/w x 30 min (13-15 based on BORG Scale).	VO_2 Peak	VO_2 peak: Control Group =Increased 3,1 ml/kg/min. Home Exercise Group =Increased 6,4 ml/kg/min

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; VO_2 : 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[34]. 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[7] (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[7]. More recently, Galán-Arriola *et al.*,[35] have identified by serial multiparametric cardiac Magnetic Resonance, intracardiomyocyte edema in T2 mapping as the earliest marker of anthracycline cardiotoxicity, in the absence of T1 mapping, extracellular volume or left ventrical 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[36]. 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)[16,37].
- Disorder and dysfunction, both at a structural and contractile level, of the Myosin heavy chain (MHC)[24,38,39].
- Disorder and Dysfunction in the Tyrosine Kinase protein[40,41].
- Excess of production of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS)[18,19].
- Deficiency and mitochondrial dysfunction[17,42,43].

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.

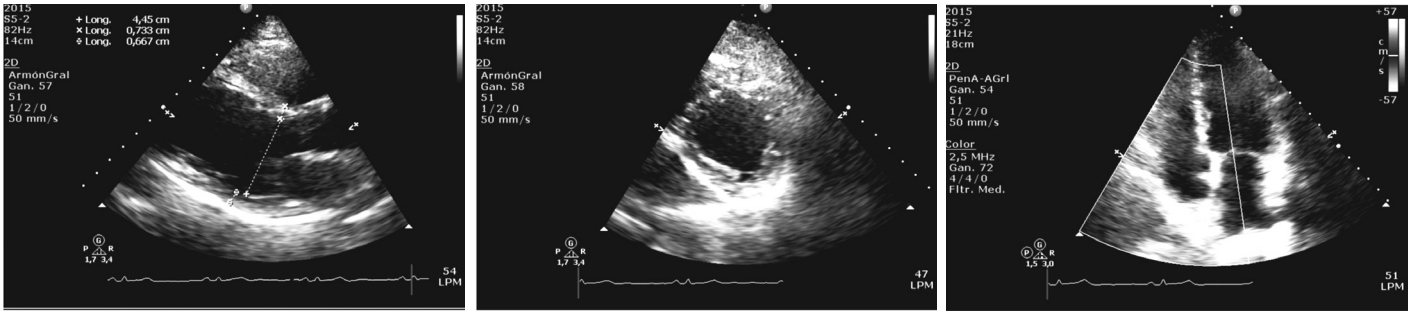
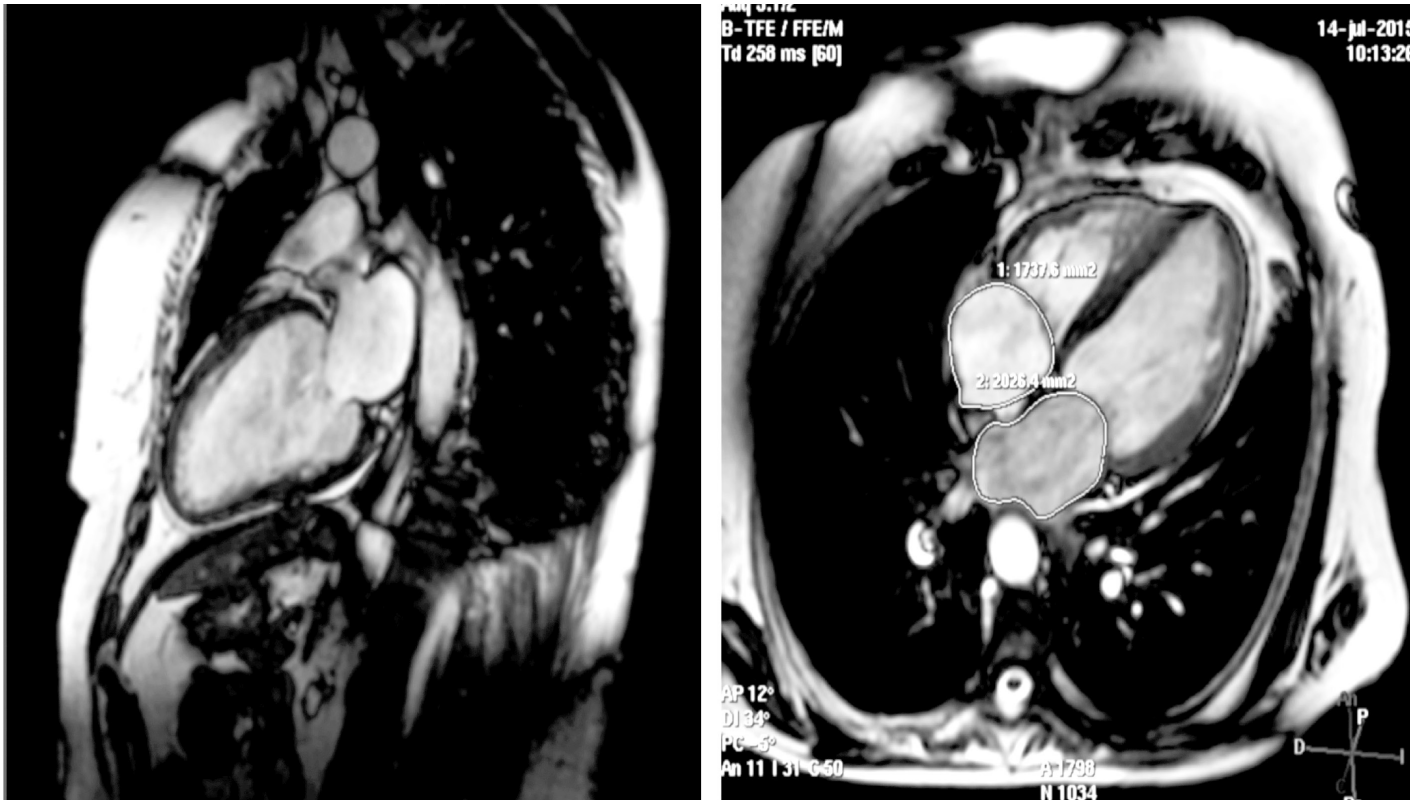


Figure 4. Cardiac Magnetic Resonance Imaging to evaluate function, morphology and viability.



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[30,32]. 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:

- The levels of strength developed by the patients outside the CRU are higher to those developed inside the hospital units[47]. Thus, the goal of minimize the risk of accident by performing the higher intensity strength work into the CRU is questioned and encourages us to promote individualized exercise units that include strength exercise in cancer patients.
- 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[48]. 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[49-51], 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)[52]. This could be extrapolated to oncological patients with risk of CTC due to the treatments.

The World Health Organization[53] included specific strength work in its guides 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[54]. Later on, the first guide that linked physical exercise and oncology was developed[54]. More recently, the experts in the delivery of exercise-based interventions in cancer patients recommend combined interventions, comprising cardiovascular and strength training[55].

Strength training components may yield very beneficial effects in cancer patients[56-58] improvements in cardiovascular function, increases in VO_2peak, 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[59], 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[60], but also for 26 different chronic diseases[61]. 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[15].

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.

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