

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

David García-González¹, Txomin Pérez-Bilbao^{1,2}, Alejandro de la Torre-Luque³, Escarlata López Ramírez, Jesús García-Foncillas López^{4,5*}, Alejandro F. San Juan^{1*}

¹Departamento de Salud y Rendimiento Humano, Facultad de Ciencias de la Actividad Física y del Deporte-INEF, Universidad Politécnica de Madrid (UPM), Madrid, Spain. ²CES Don Bosco University, Department of Physical Education, Madrid, Spain. ³Centre for Biomedical Research in Mental Health (CIBERSAM), Department of Psychiatry, Autonomous University of Madrid (UAM), Madrid, Spain. ⁴School of Medicine, Autonomous University of Madrid (UAM), Madrid, Spain. ⁵Department of Oncology, Cancer Institute, University Hospital "Fundación Jiménez Díaz", Autonomous University of Madrid (UAM), Madrid, Spain. *Sharing senior authorship.

Recibido: Summary Aceptado:

Key words:
Cardiovascular disease.
Cancer. Cardiotoxicity.
Exercise & Cardio-Oncology
Rehabilitation.

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.

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

Resumen

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

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 cardíacas 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.

SEMED-FEMEDE research Award of the year 2019

Correspondencia: Txomin Perez-Bilbao
E-mail: tperez@escuelaprofesionaldonbosco.com

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 death¹. In turn, cardiovascular disease (CVD) is the leading cause of long-term morbidity and death among cancer survivors, after second malignancies².

Cardiotoxicity is defined by the National Cancer Institute as "toxicity that affects the heart". No single, universal 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 baseline³. Heart structure dysfunction, 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 cardiomyopathy⁶.

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 therapy⁹, and monoclonal antibodies and CTC⁸. Likewise, some studies have stress the association of radiotherapy exposure (Figure 1) and CTC⁷⁻¹⁰.

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 endorsed¹¹. 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 programs¹⁴. In this line, the American Heart Association (AHA) suggests the implementation of tailored exercise for Cardio-Oncology Rehabilitation¹⁵.

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 function¹⁶. Moreover, physical exercise may contribute antioxidant agents to be produced and mitochondrial function be improved¹⁷⁻¹⁹. 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 CTC²⁰⁻²². 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.

Methods

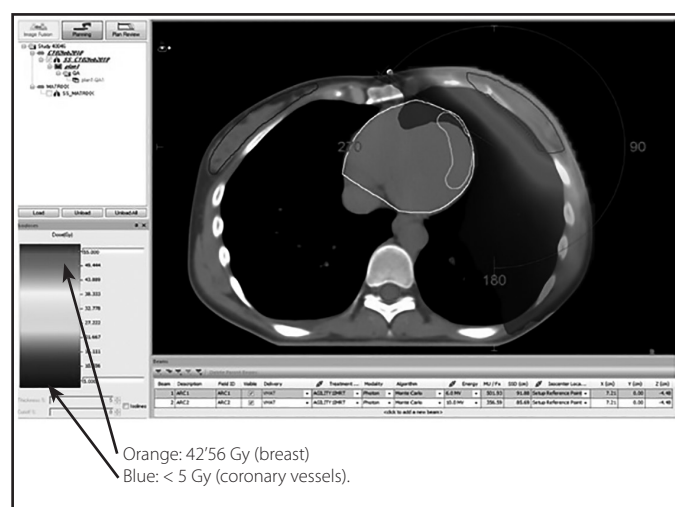
Search strategy and article selection criteria

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;

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



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_2 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.

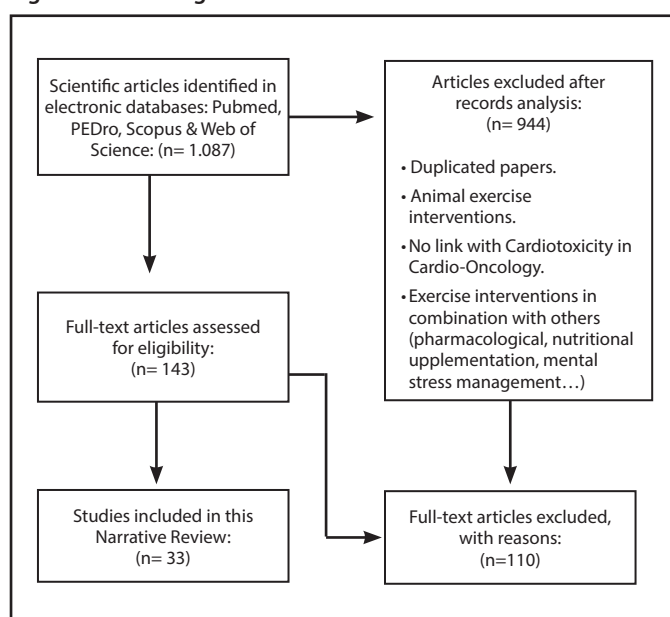
Data extraction and quality assessment

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_2 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 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 rodents²⁷⁻³¹.

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 model³⁰.

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 <i>et al</i>	242	49.2	Breast	I-III A	CV vs. ST	Aerobic Exercise Group: 3 days/w; intensity: 60-80% from maximal VO ₂ per 15-45 min. Resistance Training: 3 days/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 <i>et al</i>	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 <i>et al</i>	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 <i>et al</i>	242	49.2	Breast	II-III A	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 <i>et al</i>	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 <i>et al</i>	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 <i>et al</i>	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.

(keep going)

Study	Sample size	Mean age	Cancer site	Severity	Type of intervention	Intervention particularities	Outcome	Results
Kim <i>et al</i>	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 decreases in resting HR and resting systolic BP.
Kirkham <i>et al</i>	24	50.5	Breast	I-III	CV	A single session of 45-min treadmill exercise (intensity: 70% from HR reserve).	Cardiac biomarkers (NT-proBNP, 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 <i>et al</i>	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 <i>et al</i>	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 <i>et al</i>	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 <i>et al</i>	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 <i>et al</i>	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 <i>et al</i>	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 <i>et al</i>	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.

(keep going)

Study	Sample size	Mean age	Cancer site	Severity	Type of intervention	Intervention particularities	Outcome	Results
Survivor samples								
Adams <i>et al</i>	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 artery morphology. Brachial artery flow-mediated dilation	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.
Brdareski <i>et al</i>	18	50.5	Breast	I-III A	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 <i>et al</i>	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 <i>et al</i>	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 <i>et al</i>	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 <i>et al</i>	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 <i>et al</i>	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 <i>et al</i>	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 <i>et al</i>	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.

(keep going)

Study	Sample size	Mean age	Cancer site	Severity	Type of intervention	Intervention particularities	Outcome	Results
Musanti <i>et al</i>	42	50.5	Breast	I-III B	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 <i>et al</i>	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: Control Group = Increased 15%. Exercise Group = Increased 32%
Rahnama <i>et al</i>	29	Range: 50-65 years old	Breast	I-III B	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 <i>et al</i>	41	53	Breast	I-III A	CV	Combined individual and collective group aerobic exercise group.	VO ₂ Peak.	No significant between-group differences reported.
Rogers <i>et al</i>	222	54.4	Ductal Carcinoma & breast	I-III A	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 <i>et al</i>	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, VO ₂ peak increased by 13% in this condition.
Thorsen <i>et al</i>	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; 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, hormone therapy 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 tools³⁴. 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 myocardium⁷ (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 far⁷. More recently, Galán-Arriola *et al.*,³⁵ have identified by serial multiparametric cardiac Magnetic Resonance, intracardiomycocyte edema in T2 mapping as the earliest marker of anthracycline cardiotoxicity, in the absence of T1 mapping, extracellular volume or left ventricular 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 inflammation³⁶. 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 cardiomyopathy as a consequence of doxorubicin, trastuzumab and radiotherapy treatment for breast cancer.

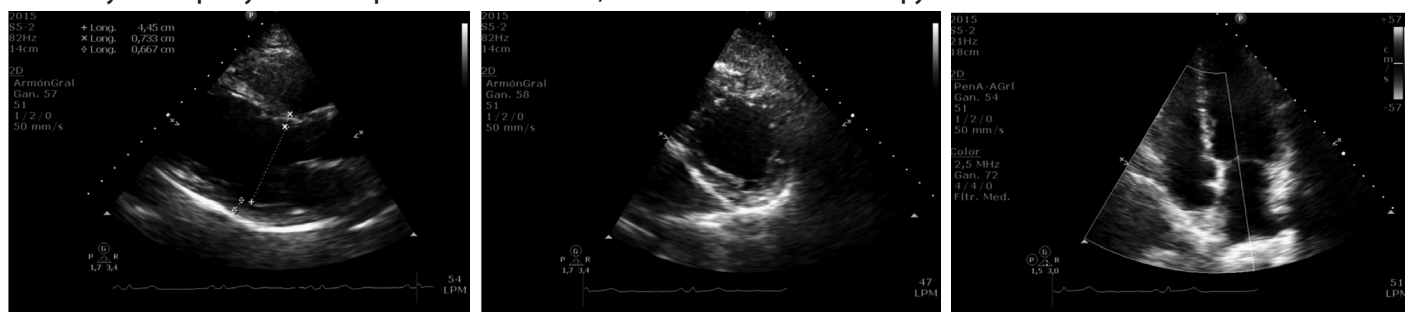
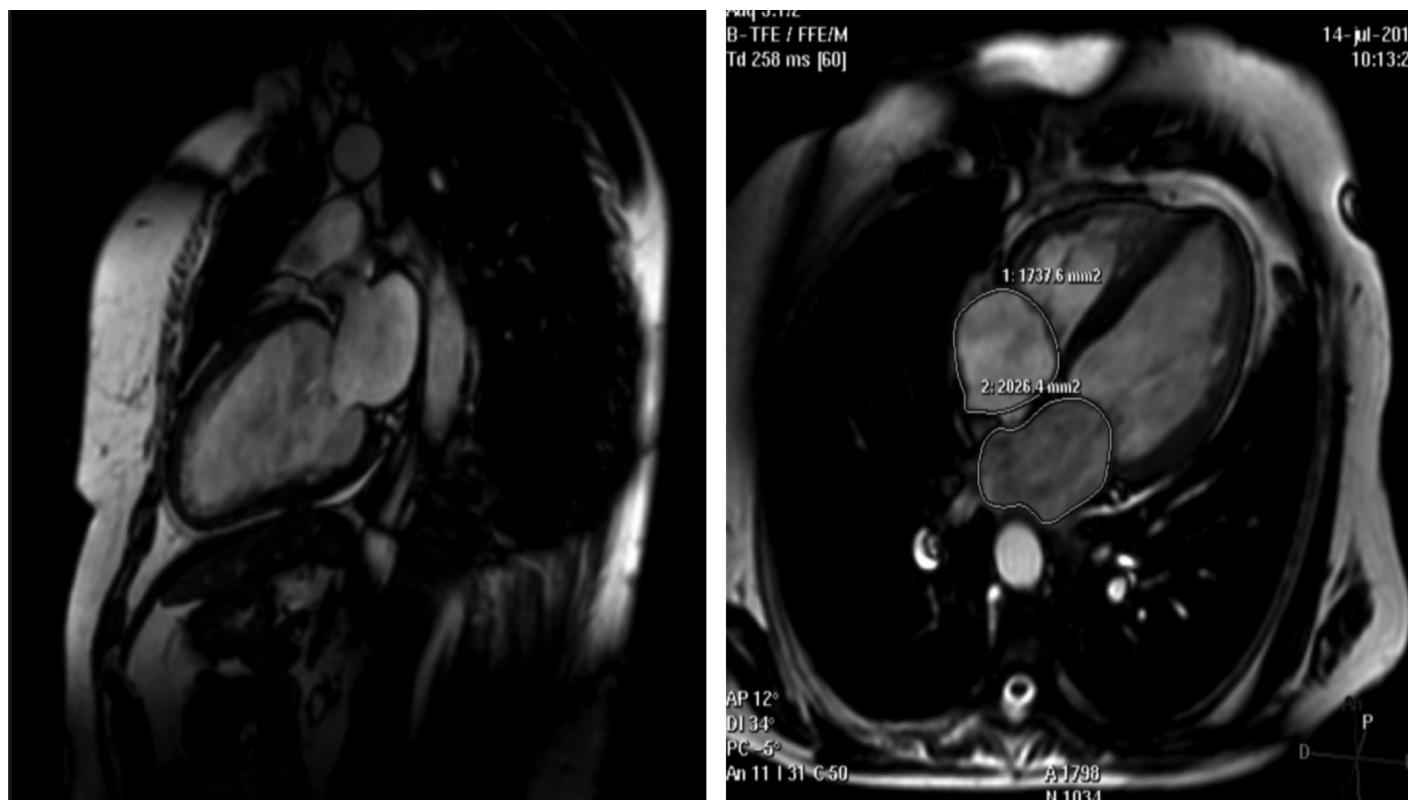


Figure 4. Cardiac Magnetic Resonance Imaging to evaluate function, morphology and viability.



Left ventricle lightly dilated and global hypokinesia 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 units⁴⁷. 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 technique⁴⁸. It is also considered the gold standard for assessing muscle strength in non-laboratory situations⁴⁸. 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 patients⁴⁹⁻⁵¹, 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 Organization⁵³ 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 used⁵⁴. Later on, the first guide that linked physical exercise and oncology was developed⁵⁴. More recently, the experts in the delivery of exercise-based interventions in cancer patients recommend combined interventions, comprising cardiovascular and strength training⁵⁵.

Strength training components may yield very beneficial effects in cancer patients⁵⁶⁻⁵⁸ improvements in cardiovascular function, increases in VO₂ 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 organ⁵⁹, 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 treatment⁶⁰, but also for 26 different chronic diseases⁶¹. 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 Statement¹⁵.

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

- Velásquez CA, González M, Berrouet MC, Jaramillo N. Cardiotoxicidad inducida por la quimioterapia desde las bases moleculares hasta la perspectiva clínica. *Rev Colomb Cardiol*. 2016;23:104-11.
- Daher IN, Daigle TR, Bhatia N, Durand JB. The prevention of cardiovascular disease in cancer survivors. *Tex Hear Inst J*. 2012;39:190-8.
- Shah CP, Moreb JS. Cardiotoxicity due to targeted anticancer agents: A growing challenge. *Ther Adv Cardiovasc Dis*. 2019; 13:1753944719843435.
- Conway A, McCarthy AL, Lawrence P, Clark RA. The prevention, detection and management of cancer treatment-induced cardiotoxicity: A meta-review. *BMC Cancer*. 2015;15:366.
- Coumbe BGT, Groarke JD. Cardiovascular autonomic dysfunction in patients with cancer. *Curr Cardiol Rep*. 2018;20:69.
- Han X, Zhou Y, Liu W. Precision cardio-oncology: Understanding the cardiotoxicity of cancer therapy. *NPJ Precis Oncol*. 2017;1:31.
- Levis BE, Binkley PF, Shapiro CL. Cardiotoxic effects of anthracycline-based therapy: What is the evidence and what are the potential harms? *Lancet Oncol*. 2017;18:e445-e456.
- Valachis A, Nilsson C. Cardiac risk in the treatment of breast cancer: Assessment and management. *Breast Cancer Targets Ther*. 2015;7:21-35.
- Heidenreich PA, Kapoor JR. Radiation induced heart disease. *Heart*. 2009;95:252-8.
- Filipei J, Frishman W. Radiation-induced heart disease. *Cardiol Rev*. 2012;20:184-8.
- Campia U, Barac A. Exercise and aerobic fitness to reduce cancer-related cardiovascular toxicity. *Curr Treat Options Cardiovasc Med*. 2016;18:44.
- Sandercock G, Hurtado V, Cardoso F. Changes in cardiorespiratory fitness in cardiac rehabilitation patients: A meta-analysis. *Int J Cardiol*. 2013;167:894-902.
- Van Deel ED, Octavia Y, de Waard MC, de Boer M, Duncker DJ. Exercise training has contrasting effects in myocardial infarction and pressure overload due to divergent endothelial nitric oxide synthase regulation. *Int J Mol Sci*. 2018;19.
- Armenian S, Bhatia S. Predicting and preventing anthracycline-related cardiotoxicity. *Am Soc Clin Oncol Educ Book*. 2018;38:3-12.
- Gilchrist SC, Barac A, Ades PA, Alfano CM, Franklin BA, Jones LW, et al. Cardio-oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: A scientific statement from the American heart association. *Circulation*. 2019; 139:e997-e1012.
- Lu L, Mei DF, Gu AG, Wang S, Lentzner B, Gustin DE, et al. Exercise training normalizes altered calcium-handling proteins during development of heart failure. *J Appl Physiol*. 2002;92:1524-30.
- Marques-Aleixo I, Santos-Alves E, Torrella JR, Oliveira PJ, Magalhaes J, Ascensao A. Exercise and doxorubicin treatment modulate cardiac mitochondrial quality control signaling. *Cardiovasc Toxicol*. 2018;18:43-55.
- Roy K, Wu Y, Meitzler JL, Juhasz A, Liu H, Jiang G, et al. NADPH oxidases and cancer. *Clin Sci*. 2015;128:863-75.
- Szatrowski TP, Nathan CF. Production of large amounts of hydrogen peroxide by human tumor cells. *Cancer Res*. 1991;51:794-8.
- Scott JM, Khakoo A, MacKey JR, Haykowsky MJ, Douglas PS, Jones LW. Modulation of anthracycline-induced cardiotoxicity by aerobic exercise in breast cancer: Current evidence and underlying mechanisms. *Circulation*. 2011;124:642-50.
- Chen JJ, Wu PT, Middlekauff HR, Nguyen KL. Aerobic exercise in anthracycline-induced cardiotoxicity: A systematic review of current evidence and future directions. *Am J Physiol Circ Physiol*. 2016;312:H213-H222.
- Scott JM, Nilsen TS, Gupta D, Jones LW. Exercise therapy and cardiovascular toxicity in cancer. *Circulation*. 2018;137:1176-91.
- Bredahl EC, Pfannenstiel KB, Quinn CJ, Hayward R, Hydock DS. Effects of Exercise on doxorubicin-induced skeletal muscle dysfunction. *Med Sci Sport Exerc*. 2016;48:1468-73.
- Pfannenstiel K, Hayward R. Effects of resistance exercise training on doxorubicin-induced cardiotoxicity. *J Cardiovasc Pharmacol*. 2018;71:332-9.
- Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62:242-74.
- Cormie P, Atkinson M, Bucci L, Cust A, Eakin E, Hayes S, et al. Clinical oncology society of Australia position statement on exercise in cancer care. *Med J Aust*. 2018;209:184-7.
- Ascensao A, Magalhaes J, Soares JM, Ferreira R, Neuparth MJ, Marques F, et al. Moderate endurance training prevents doxorubicin-induced in vivo mitochondriopathy and reduces the development of cardiac apoptosis. *Am J Physiol Heart Circ Physiol*. 2005;289:H722-H731.
- Chicco AJ, Schneider CM, Hayward R. Exercise training attenuates acute doxorubicin-induced cardiac dysfunction. *J Cardiovasc Pharmacol*. 2006;47:182-9.
- Smuder AJ, Kavazis AN, Min K, Powers SK. Doxorubicin-induced markers of myocardial autophagic signaling in sedentary and exercise trained animals. *J Appl Physiol*. 2013;115:176-85.
- Wonders KY, Hydock DS, Schneider CM, Hayward R. Acute exercise protects against doxorubicin cardiotoxicity. *Integr Cancer Ther*. 2008;7:147-54.
- Jacquinet Q, Meneveau N, Chatot M, Bonnetain F, Degano B, Bouhaddi M, et al. A phase 2 randomized trial to evaluate the impact of a supervised exercise program on cardiotoxicity at 3 months in patients with her2 overexpressing breast cancer undergoing adjuvant treatment by trastuzumab: Design of the cardapac study. *BMC Cancer*. 2017;17:425.
- Kirkham AA, Shave RE, Bland KA, Bovard JM, Eves ND, Gelmon KA, et al. Protective effects of acute exercise prior to doxorubicin on cardiac function of breast cancer patients: A proof-of-concept rct. *Int J Cardiol*. 2017;245:263-70.
- Haykowsky MJ, Mackey JR, Thompson RB, Jones LW, Paterson DL. Adjuvant trastuzumab induces ventricular remodeling despite aerobic exercise training. *Clin Cancer Res*. 2009;15:4963-7.
- Todaro MC, Oretto L, Qamar R, Paterick TE, Carerj S, Khandheria BK. Cardioncology: State of the heart. *Int J Cardiol*. 2013;168:680-7.
- Galán-Arriola C, Lobo M, Vilchez-Tschischke JP, López GJ, de Molina-Iracheta A, Pérez-Martínez C, et al. Serial magnetic resonance imaging to identify early stages of anthracycline-induced cardiotoxicity. *J Am Coll Cardiol*. 2019;73:779-91.
- Ruiz-Casado A, Martín-Ruiz A, Pérez LM, Provencio M, Fiuza-Luces C, Lucia A. Exercise and the hallmarks of cancer. *Trends in Cancer*. 2017;3:423-41.
- Hanna AD, Lam A, Tham S, Dulhunty AF, Beard NA. Adverse effects of doxorubicin and its metabolic product on cardiac r y r2 and serca2a. *Mol Pharmacol*. 2014; 86: 438-49.
- Hydock DS, Lien C-Y, Schneider CM, Hayward R. Effects of voluntary wheel running on cardiac function and myosin heavy chain in chemically gonadectomized rats. *Am J Physiol Circ Physiol*. 2007;293:H3254-H3264.
- Hydock DS, Lien CY, Schneider CM, Hayward R. Exercise preconditioning protects against doxorubicin-induced cardiac dysfunction. *Med Sci Sport Exerc*. 2008;40:808-17.
- Orphanos GS, Ioannidis GN, Ardavanis AG. Cardiotoxicity induced by tyrosine kinase inhibitors. *Acta Oncol Madr*. 2009;48:964-70.
- Vermaete N, Wolter P, Verhoeve G, Gosselink R. Physical activity, physical fitness and the effect of exercise training interventions in lymphoma patients: A systematic review. *Ann Hematol*. 2013;92:1007-21.
- Zhou S, Starkov A, Froberg MK, Leino RL, Wallace KB. Cumulative and irreversible cardiac mitochondrial dysfunction induced by doxorubicin. *Cancer Res*. 2001;61:771-7.
- Wallace KB. Adriamycin-induced interference with cardiac mitochondrial calcium homeostasis. *Cardiovasc Toxicol*. 2007;7:101-7.
- Gibson NM, Greufe SE, Hydock DS, Hayward R. Doxorubicin-induced vascular dysfunction and its attenuation by exercise preconditioning. *J Cardiovasc Pharmacol*. 2013;62:355-60.
- Jensen BT, Lien CY, Hydock DS, Schneider CM, Hayward R. Exercise mitigates cardiac doxorubicin accumulation and preserves function in the rat. *J Cardiovasc Pharmacol*. 2013;62:263-9.
- Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary running suppresses tumor growth through epinephrine- and il-6-dependent nk cell mobilization and redistribution. *Cell Metab*. 2016;23:554-62.
- Adams J, Cline M, Reed M, Masters A, Ehle K, Hartman J. Importance of resistance training for patients after a cardiac event. *Proc Bayl Univ Med Cent*. 2006;19:246-8.
- Seo DI, Kim E, Fahs CA, Rossow L, Young K, Ferguson SL, et al. Reliability of the one-repetition maximum test based on muscle group and gender. *J Sports Sci Med*. 2012;11:221-5.
- Crozier Ghilarducci LE, Holly RG, Amsterdam EA. Effects of high resistance training in coronary artery disease. *Am J Cardiol*. 1989;64:866-70.
- Beniamini Y, Rubenstein JJ, Zaichkowsky LD, Crim MC. Effects of high-intensity strength training on quality-of-life parameters in cardiac rehabilitation patients. *Am J Cardiol*. 1997;80:841-6.
- Karlsen T, Helgerud J, Støylen A, Lautitsen N, Hoff J. Maximal strength training restores walking mechanical efficiency in heart patients. *Int J Sport Med*. 2009;30:337-42.
- Volakis KA, Tokmakidis SP. Resistance Exercise training in patients with heart failure. *Sport Med*. 2005;35:1085-103.

53. World Health Organization. World recommendations on physical activity for health. 2010.
54. Winningham ML, MacVicar MG, Burke CA. Exercise for cancer patients: guidelines and precautions. *Phys Sportsmed*. 1986;14:125-34.
55. De Backer IC, Schep G, Backx FJ, Vreugdenhil G, Kuipers H. Resistance training in cancer survivors: A systematic review. *Int J Sport Med*. 2009;30:703-12.
56. Volaklis KA, Halle M, Meisinger C. Muscular strength as a strong predictor of mortality: A narrative review. *Eur J Intern Med*. 2015;26:303-10.
57. Strasser B, Steindorf K, Wiskemann J, Ulrich CM. Impact of resistance training in cancer survivors: A meta-analysis. *Med Sci Sport Exerc*. 2013;45:2080-90.
58. Serra MC, Ryan AS, Ortmeier HK, Addison O, Goldberg AP. Resistance training reduces inflammation and fatigue and improves physical function in older breast cancer survivors. *Menopause*. 2018;25:211-6.
59. Giudice J, Taylor JM. Muscle as a paracrine and endocrine organ. *Curr Opin Pharmacol*. 2017;34:49-55.
60. Dethlefsen C, Pedersen KS, Hojman P. Every exercise bout matters: Linking systemic exercise responses to breast cancer control. *Breast Cancer Res Treat*. 2017;162:399-408.
61. Pedersen BK, Saltin B. Exercise as medicine – Evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports*. 2015;25:1-72.

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

- MacVicar MG, Winingham ML, Nickel JL. Effects of aerobic interval training on cancer patient's functional capacity. *Nurs Res*. 1989;38(6):348-51.
- Segal R, Evans W, Johnson D, Smith J, Colletta S, Gayton J, et al. Structured exercise improves physical functioning in women with stages I and II breast cancer: Results of a randomized controlled trial. *J Clin Oncol*. 2001;19(3):657-65.
- Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial. *J Clin Oncol*. 2007;25(28):4396-404.
- Courneya KS, Sellar CM, Stevinson C, McNeely ML, Peddle CJ, Friedenreich CM, et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *J Clin Oncol*. 2009;27(27):4605-12.
- Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol*. 2009;27(3):344-51.
- Courneya KS, McKenzie DJ, Mackey JR, Gelmon K, Friedenreich CM, Yasui Y, et al. Effects of exercise dose and type during breast cancer chemotherapy: Multicenter randomized trial. *J Natl Cancer Inst*. 2013;105(23):1821-32.
- Jones LW, Fels DR, West M, Allen JD, Broadwater G, Barry WT, et al. Modulation of circulating angiogenic factors and tumor biology by aerobic training in breast cancer patients receiving neoadjuvant chemotherapy. *Cancer Prev Res (Phila)*. 2013;6(9):925-37.
- Van Waart H, Stuiver MM, Van Harten WH, Geleijn E, Kieffer JM, Buffart LM, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy completion rates: Results of the paces randomized clinical trial. *J Clin Oncol*. 2015;33(17):1918-27.
- Scott JM, Nilsen TS, Gupta D, Jones LW. Exercise therapy and cardiovascular toxicity in cancer. *Circulation*. 2018;137(11):1176-1191.
- Kirkham AA, Shave RE, Bland KA, Bovard JM, Eves ND, Gelmon KA, et al. Protective effects of acute exercise prior to doxorubicin on cardiac function of breast cancer patients: A proof of concept RCT. *Int J Cardiol*. 2017;245:263-270.
- Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: Cardiopulmonary and quality of life outcomes. *J Clin Oncol*. 2003;21(9):1660-8.
- Thorsen L, Skovlund E, Stromme SB, Hornslien K, Dahl AA, Fossa SD. Effectiveness of physical activity on cardiorespiratory fitness and health-related quality of life in young and middle-aged cancer patients shortly after chemotherapy. *J Clin Oncol*. 2005;23(10):2378-88.
- Pinto BM, Papandonatos GD, Goldstein MG, Marcus BH, Farrell N. Home-based physical activity intervention for colorectal cancer survivors. *Psychooncology*. 2013;22(1):54-64.
- Jones LW, Douglas PS, Khouri MG, Mackey JR, Wojdyla D, Kraus WE, et al. Safety and efficacy of aerobic training in patients with cancer who have heart failure: An analysis of the hf-action randomized trial. *J Clin Oncol*. 2014;32(23):2496-502.
- Jones LW, Hornsby WE, Freedland SJ, Lane A, West MJ, Moul JW, et al. Effects of nonlinear aerobic training on erectile dysfunction and cardiovascular function following radical prostatectomy for clinically localized prostate cancer. *Eur Urol*. 2014;65(5):852-5.
- Rogers LQ, Courneya KS, Anton PM, Hopkins-Price P, Verhulst S, Vicari SK, et al. Effects of the BEAT cancer physical activity behavior change intervention on physical activity, aerobic fitness, and quality of life in breast cancer survivors: A multicenter randomized controlled trial. *Breast Cancer Res Treat*. 2015;149(1):109-19.
- Adams SC, Delorey DS, Davenport MH, Stickland MK, Fairey AS, North S, et al. Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: A phase 2 randomized controlled trial. *Cancer*. 2017;123(20):4057-4065.
- Haykowsky MJ, Mackey JR, Thompson RB, Jones LW, Paterson DL. Adjuvant trastuzumab induces ventricular remodeling despite aerobic exercise training. *Clin Cancer Res*. 2009;15(15):4963-7.
- Hornsby WE, Douglas PS, West MJ, Kenjale AA, Lane AR, Schwitzer ER, et al. Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: A phase II randomized trial. *Acta Oncol*. 2014;53(1):65-74.
- Kim CJ, Kang DH, Smith BA, Landers KA. Cardiopulmonary responses and adherence to exercise in women newly diagnosed with breast cancer undergoing adjuvant therapy. *Cancer Nurs*. 2006;29(2):156-65.
- Brdaeski Z, Djurovic A, Susnjak S, Zivotic-Vanovic M, Ristic A, Konstantinovic L, et al. Effects of a short-term differently dosed aerobic exercise on maximum aerobic capacity in breast cancer survivors: A pilot study. *Vojnosanit Pregl*. 2012;69(3):237-42.
- Dolan LB, Gelmon K, Courneya KS, Mackey JR, Segal RJ, Lane K, et al. Hemoglobin and aerobic fitness changes with supervised exercise training in breast cancer patients receiving chemotherapy. *Cancer Epidemiol Biomarkers Prev*. 2010;19(11):2826-32.
- Herrero F, San Juan AF, Fleck SJ, Balmer J, Pérez M, Cañete S, et al. Combined aerobic and resistance training in breast cancer survivors: A randomized, controlled pilot trial. *Int J Sports Med*. 2006;27(7):573-80.
- Herrero F, San Juan AF, Fleck SJ, Foster C, Lucía A. Effects of detraining on the functional capacity of previously trained breast cancer survivors. *Int J Sports Med*. 2007;28(3):257-64.
- Hsieh CC, Sprod LK, Hydock DS, Carter SD, Hayward R, Schneider CM. Effects of a supervised exercise intervention on recovery from treatment regimens in breast cancer survivors. *Oncol Nurs Forum*. 2008;35(6):909-15.
- Hutnick NA, Williams NI, Kraemer WJ, Orsega-Smith E, Dixon RH, Bleznak AD, et al. Exercise and lymphocyte activation following chemotherapy for breast cancer. *Med Sci Sports Exerc*. 2005;37(11):1827-35.
- Kolden GG, Strauman TJ, Ward A, Kuta J, Woods TE, Schneider KL, et al. A pilot study of group exercise training (GET) for women with primary breast cancer: Feasibility and Health benefits. *Psychooncology*. 2002;11(5):447-56.
- Ligibel JA, Partridge A, Giobbie-Hurder A, Campbell N, Shockro L, Salinardi T, et al. Physical and psychological outcomes among women in a telephone-based exercise intervention during adjuvant therapy for early stage breast cancer. *J Womens Health (Larchmt)*. 2010;19(8):1553-9.
- Musanti R. A study of exercise modality and physical self-esteem in breast cancer survivors. *Med Sci Sports Exerc*. 2012;44(2):352-61.
- Rahnama N, Nouri R, Rahmani F, Damirchi A, Emami H. The effects of exercise training on maximum aerobic capacity, resting heart rate, blood pressure and anthropometric variables of postmenopausal women with breast cancer. *J Res Med Sci*. 2010;15(2):78-83.
- Rogers LQ, Hopkins-Price P, Vicari S, Pamentier R, Courneya KS, Markwell S, et al. A randomized trial to increase physical activity in breast cancer survivors. *Med Sci Sports Exerc*. 2009;41(4):935-46.
- Schneider CM, Hsieh CC, Sprod LK, Carter SD, Hayward R. Effects of supervised exercise training on cardiopulmonary function and fatigue in breast cancer survivors during and after treatment. *Cancer*. 2007;110(4):918-25.
- Vincent F, Labourey JL, Leobon S, Antonini NT, Lavau-Denes S, Tubiana-Mathieu N. Effects of a home-based walking training program in cardiorespiratory fitness in breast cancer patients receiving adjuvant chemotherapy: A pilot study. *Eur J Phys Rehabil Med*. 2013;49(3):319-29.