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Review article

Protective effects of exercise on cardiotoxicity induced by breast cancer treatments: A systematic review and meta-analysis

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ABSTRACT

Objective: Currently, one of the main causes of death in women with breast cancer is cardiovascular disease caused by the oncologic therapies. Exercise has demonstrated positive effects on cardiovascular fitness in individuals without cancer. Therefore, the aim of this study was to evaluate the cardioprotective effects of exercise in women with breast cancer, during and after the application of their treatments.
Methods: Systematic search was done in PubMed, Scopus, Web of Science, CINAHL, MEDLINE, SPORTDiscus, and PEDro. The articles must have been published in the last ten years; the intervention to be evaluated was to consist of an exercise program; the sample had to comprise women who were undergoing breast cancer treatment or who had completed it at the time of the intervention; and the outcome variables had to include at least one parameter for the assessment of cardiac function and/or structure.
Results: Of the 28 articles identified, nine reported non-randomized controlled studies, 16 randomized clinical trials and three quasi-experimental studies. The effects of exercise on left ventricular ejection fraction, global longitudinal strain and the E/A waveforms ratio were not significant. However, its effect on VO_2max was significant.
Conclusions: Exercise does not seem to be effective in avoiding the cardiotoxic effects of oncological treatment for breast cancer. Although exercise seems to mitigate the symptomatology, reflected in improved functional capacity, more long-term studies are needed.
PROSPERO registration code: CRD42023391441

1. Introduction

Breast cancer (BC) is the most commonly diagnosed carcinoma in the world, with >2.26 million new cases in 2020 [1]. However, unlike the other tumor types, BC mortality has been decreasing in recent years [2].

Advances in oncologic diagnosis and treatment of BC are responsible for this increase in survival. But chemotherapy, endocrine therapy and radiotherapy are not without risks such as cardiotoxicity (CT) [3]. CT refers to the changes produced in cardiac function and structure, which can manifest both acutely and in the long term, induced by these adjuvant and/or neoadjuvant BC therapies [4–6]. Even so, CT is one of the more frequent and potentially serious cancer therapy related side effects which affects the quality of life and mortality in breast cancer survivors [7].

The most commonly used chemotherapeutic agents are anthracyclines (such as doxorubicin and epirubicin), whose adverse effects are dose-dependent [8,9]. As well as trastuzumab, a monoclonal antibody that is administered for human epidermal growth factor receptor-positive BCs and is often combined with anthracyclines [10]. Tamoxifen and aromatase inhibitors are the endocrine therapy of choice, in premenopausal and postmenopausal women, respectively. These are hormonal treatments that are applied for at least 5 years [5]. Finally, the sequelae produced by radiotherapy are also dose-dependent, and it has been shown that the cumulative incidence of acute coronary syndrome

Abbreviations: BC, breast cancer; CI, confidence intervals; CT, cardiotoxicity; MD, mean differences; PERSiST, PRISMA recommendations for their implementation in Exercise, Rehabilitation, Sport Medicine and Sports Science.; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; VO_2max, maximal oxygen consumption.

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increases by 16.5 % per Grey administered within 9 years of radiotherapy [11,12]. Additionally, all these therapies can be combined, which increases the probability of developing CT [5].

The European Society of Cardiology and the American Heart Association have developed guidelines for the treatment and care of these women with the aim of minimizing CT [5,7]. Both reflect that, in the last decade, both the prevention and treatment of CT is being addressed with various lines of research (especially with drugs or exercise) [5,7]. Furthermore, it is important to keep in mind that CT is not the only side effect produced by these treatments. These patients encounter a long list of very limiting symptoms: fatigue, nausea, pain, anxiety, depression, lymphedema or decreased quality of life, sleep difficulties, increased risk of falls, osteoporosis, neuropathies or alterations in cognitive functions; among others [13,14]. The decrease in functional capacity, whose most sensitive marker is maximal oxygen consumption (VO_2max) [15,16], is strongly related to cardiotoxicity. This is, moreover, a predictor of cardiovascular death [15,17,18]. As a consequence, it is a key indicator in cardioprotection since, taking into account the cascade of effects that occur at the cardiovascular level, this is diminished [19].

The American Cancer Society and the American College of Sports Medicine have formulated recommendations for engaging in exercise during and after cancer treatment. These recommendations have recently been endorsed by the National Comprehensive Cancer Network as well [20,21]. Exercise has demonstrated notable effects on cardiovascular reserve, hypertension, high cholesterol, obesity, and overall reductions in mortality among individuals without cancer [22]. Despite these general benefits, exercise is not explicitly addressed in clinical cardio-oncology guidelines [23,24].

Therefore, the aim of this study was to analyze the cardioprotective effect of exercise in women who are receiving and/or have completed their BC treatments.

2. Methods

2.1. Search strategy

This study was prospectively registered on PROSPERO (ID: CRD42023391441) and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), the recommendations for their implementation in Exercise, Rehabilitation, Sport Medicine and Sports Science (PERSiST) [25] and the reporting guidelines and the recommendations from the Cochrane Collaboration [26]. The PICO question was then chosen as follows: P – population: breast cancer patients and survivors; I – intervention: exercise therapy; C – control: sedentarism, usual cancer care or another intervention; O – outcome: cardiac function and/or structure; S – study designs: quantitative studies (cohort, quasi-experimental, controlled non-randomized or randomized clinical trials).

A systematic search of publications was conducted in December 2023 in the following databases: PubMed, Scopus, Web of Science, CINAHL, MEDLINE, SPORTDiscus, and PEDro. The search strategy included different combinations with the following Medical Subject Headings (MeSH) terms: *Breast neoplasm, Heart diseases, Exercise, Exercise therapy, Hemodynamics, Global longitudinal strain, Heart function tests, Cardiovascular diseases,* and *Cardiotoxicity*. Furthermore, we use free terms not included in any thesaurus: *Breast cancer, Cardiac function, Physical activity, VO_2max, Breast malignancy, Ventricular ejection* and *Cardioprotective.* The search strategy according to the focused PICOS question is presented in Table S1.

2.2. Selection criteria

After removing duplicates, two reviewers (PT. X. X.-X. and PhD. X.X.-X.) independently screened articles for eligibility. In case of disagreement, a third reviewer (PhD. X. X.-X.) finally decided whether the study should be included or not. For the selection of results, the inclusion criteria established that: (a) the articles must have been published in the last ten years (from 2012 to the present); (b) the intervention to be evaluated was to consist of an exercise program; (c) the sample had to be made up of women who were undergoing BC treatment or who had completed it at the time of the intervention; and (d) the outcome variables had to include at least one parameter for the assessment of cardiac function and/or structure.

On the other hand, studies were excluded from this review if: (a) they had a non-quantitative or experimental methodology (reviews, meta-analyses, editorials…); (b) their full text was not available; and (c) samples made up of animals.

After screening the data, extracting, obtaining and screening the titles and abstracts for inclusion criteria, the selected abstracts were obtained in full texts. Titles and abstracts lacking sufficient information regarding inclusion criteria were also obtained as full texts. Full text articles were selected in case of compliance with inclusion criteria by the two reviewers using a data extraction form.

2.3. Data collection and analysis

The two reviewers mentioned independently extracted data from included studies using a customized data extraction table in Microsoft Excel. In case of disagreement, both reviewers debated until an agreement was reached.

The data extracted from the included articles for further analysis were: demographic information (title, authors, journal and year), characteristics of the sample (age, cardiovascular risk factors, inclusion and exclusion criteria, and number of participants), study-specific parameters (study type, characteristics of the exercise program, duration of the intervention and each session, and duration of each exercise session), follow-up and dropout rates of participants, and results obtained (variables analyzed, instruments used and results throughout the follow-up). Tables were used to describe both the studies' characteristics and the extracted data.

2.4. Assessment of risk of bias

The Oxford 2011 Levels of Evidence was used to assess the methodological quality of studies. The Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool was used to assess the risk of bias in non-randomized studies [27], while the Risk of Bias (RoB) tool was used to assess the risk of bias in randomized studies [28]. Additionally, the Grades of Recommendations Assessment, Development, and Evaluation (GRADE) approach was employed to assess the quality of the evidence when conducting the meta-analysis [29].

2.5. Statistical analysis

Random and fixed effects models were used for the analysis of mean differences (MD) with their 95 % confidence intervals (CI) [30]. I^2 values higher than 50 % were considered as having substantial heterogeneity, and the random-effects model was used for analysis of the data [30]. Effect sizes were interpreted using the following cut-off values: 0–0.2 (very small); 0.2–0.5 (small); 0.5–0.8 (moderate); and $<$ 0.8 (large) [31]. The same increments were used for negative values. When these data were not available in the study they were requested via email to the authors. The significance level was set to $p < 0.05$. The analyses were performed with Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ).

3. Results

3.1. Characteristics of the selected studies

Of the 5732 total results identified, 1769 records were duplicates, so 3963 were screened for their title and abstract to see if they met the

inclusion criteria. Of these, 3692 were then excluded by applying the inclusion and exclusion criteria. Of the 271 articles screened, 28 were finally selected (Fig. 1).

Of the 28 articles, nine were non-randomized controlled studies [32–40], 16 were randomized clinical trials [41–56] and three were quasi-experimental studies [57–59]. Consequently, the evidence provided by these investigations was between levels 4 and 1b (Table 1).

3.2. Interventions and patients evaluated

25 of the interventions included aerobic exercise [32,34–39,41–49,51–59]. Of them, 13 combined it with resistance exercise [32,35,36,38,39,41,46,47,51,54–57]. However, the authors of three of the investigations did not specify the exercise implemented [33,40,50]. Those investigations that define the intensity of the exercise applied, graded it as moderate [32,35,36,41,43–45,47–49,52,53,55,57,59] or moderate-high [46,51,56].

The women studied had a diagnosis of stage I-III BC [32–47,49,50,54,55,57–59]. In addition, in two investigations they also included women with stage 0 cancer [52,53] and, in another, women with stage IV cancer [48]. There was one investigation in which only included women stage 0 cancer [56] and in another one no reference was made to the cancer stage of the patients [51].

In 25 of them, the patients had already overcome the BC and finished their treatments [32,33,36,42,45,48,51–53] or were being treated [35,36,38–41,43,44,46,47,49,50,54–56,59] and the remaining three developed during and after oncologic treatment [34,57,58]. The oncologic treatment of the patients was also different according to the study, although chemotherapy applied in all [32–60] and in most was combined with radiotherapy [32,33,35–37,40–42,45,46,50–56,58] (Table 1).

All participants were between 18 and 75 years of age [32–38,42–48,50–59]. In addition, most participants had previous cardiovascular risk factors [35–37,42–45,54,57,58] such as hypertension [36,37,43,44,57,58], diabetes mellitus [36,43,44,58], smoking [37,42,58], sedentary lifestyle [35,45,54], angina pectoris [43,44], alcoholism [42], metabolic disease [57], hyperlipidemia [58], obesity [37], arrhythmia [57], valvular prolapse [57] and/or previous acute myocardial infarction [57]. Other methodological characteristics such as inclusion and exclusion criteria are detailed in Table S2.

3.3. Effects on left ventricular ejection fraction

Six studies [34,36,38,44,47,49] analysing the variable left ventricular ejection fraction were included in the meta-analysis with a total sample size of 193 participants, all of them completed treatment. Three of them were randomized controlled studies [44,47,49]. The results indicated a non-statistically significant change in left ventricular

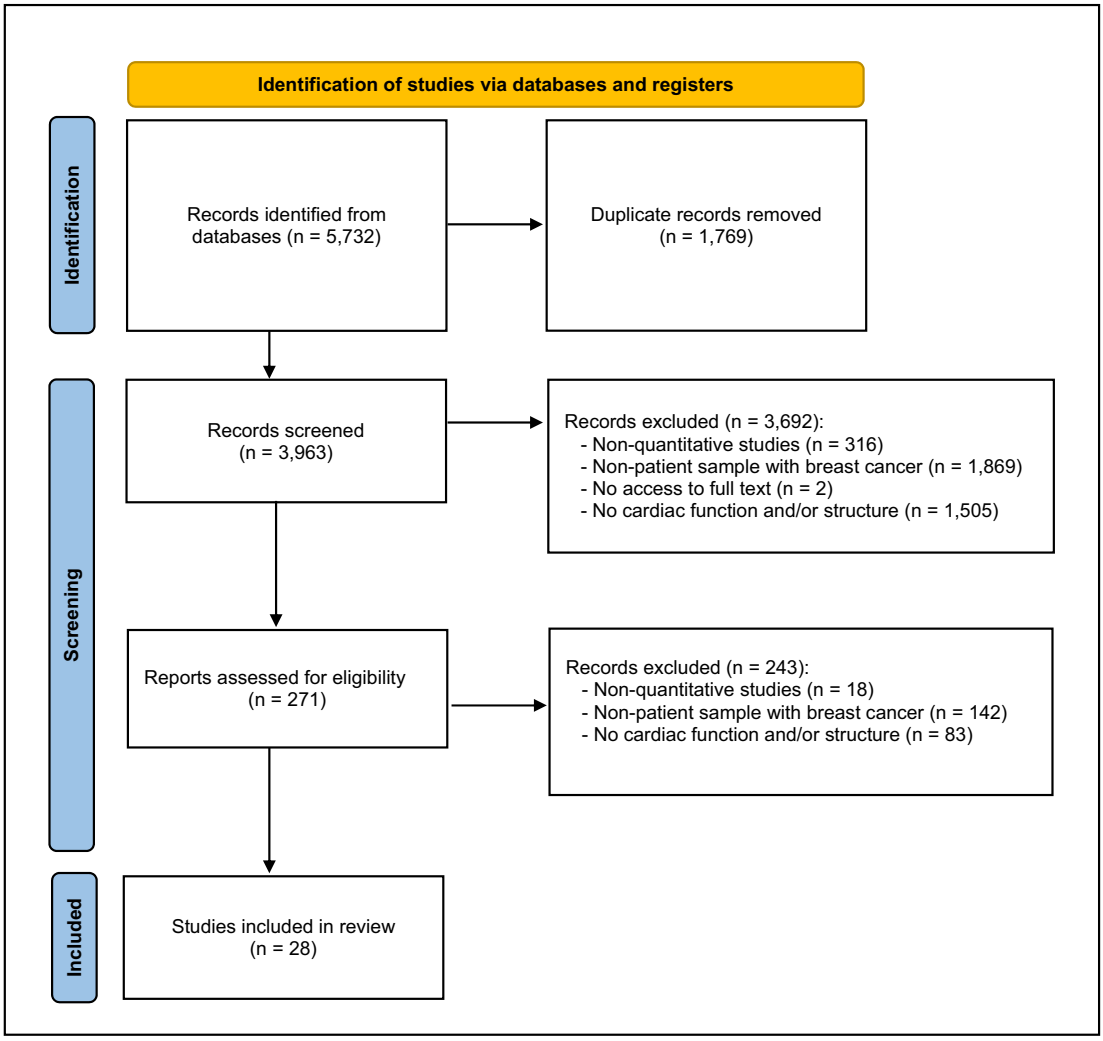


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses. (PRISMA) flow diagram.

Table 1
Methodological characteristics of the studies analyzed.

Authors	Design	Sample size	Intervention		Time of intervention (number of sessions)	Oncology treatment				LE
			Experimental group	Control group		S	CH	R	ET	
Arem et al. [41] (2016)	RCT	83	Combination of moderate-intensity aerobic and resistance training: - Brisk walking (treadmill or outside) (150 min/week) - 6 exercises performed for 8–12 repetitions for three sets. Participants progressed up to three sets per exercise over the first month.	Aerobic exercise such as stationary bicycling or brisk walking.	12 months (96)	×	✓	✓	✓	2b
Casla et al. [46] (2015)	RCT	81	Supervised aerobic and resistance exercise with increased intensity: - 10 min of warm-up (50–70 % of heart rate-reserve). - 25-30 min of aerobic exercise (55–85 % of heart rate-reserve). - 10–15 min of resistance exercise (10–20 Borg Scale). - 10 min of cool-down (stretching).	Usual behavior, without changes in their physical activity levels or diet.	3 months (24)	×	✓	✓	✓	1b
Chung et al. [47] (2022)	RCT	32	Supervised sessions of: - 40 min of aerobic exercise at 50 % of heart rate-reserve. - 15 min of resistance exercise at rated perceived exertion 13–14 (10–20 repetitions, 2–3 sets). - 5 min of flexibility training.	Usual cancer care.	3 months (24)	×	✓	×	×	1b
Dias et al. [35] (2017)	CT	18	Sessions of 70 min: - 30 min of aerobic exercise (60 % VO_2max). - 40 min of resistance exercise (between 6 and 9 Omni scale). - Stretch exercises (20–30 s each one).	*Not described*	3 months (36)	×	✓	✓	✓	2b
Foulkes et al. [39] (2019)	CT	28	Supervised sessions of: - 30 min of aerobic training. - 30 min of resistance training. Participants were also prescribed one unsupervised 30–60 min home-based aerobic exercise session per week.	Usual cancer care.	3 months (24 supervised +12 unsupervised)	×	✓	×	×	2b
Giallauria et al. [48] (2016)	RCT	51	Exercise training program and dietary program: - 5 min of warming. - 30 min of cycle or treadmill (60–70 % VO_2max). - 5 min of cooling down.	Usual cancer care.	12 months (72)	✓	✓	×	✓	1b
Hornsby et al. [49] (2014)	RCT	19	Aerobic training non-group based supervised: cycle ergometry (60–70 % peak workload) during 15–20 min.	Usual cancer care.	3 months (36)	×	✓	×	×	1b
Howden et al. [38] (2019)	CT	28	Supervised sessions of 60 min: - 30 min of aerobic training. - 30 min of resistance training. Unsupervised aerobic sessions of 30–60 min. Prescribed based on the baseline maximal exercise test and regular submaximal incremental exercise tests performed.	Usual cancer care.	5 months (40 supervised +20 unsupervised)	×	✓	×	×	2b
Jones et al. [32] (2020)	CT	51	Periodization plan followed a modified version of the 2:1 step paradigm (2 weeks of loading, 1 week unloading). Sessions of 60 min: - 5 min of warm-up. - 45 min circuit: aerobic (self-selected intensity) + endurance (60 % maximum resistance). - 10 min of cool down.	*Not described*	3 months (24)	✓	✓	✓	✓	2b
Kirkham et al. [44] (2017) Kirkham et al. [43] (2018)	RCT	24	Session of 45 min: - 10-min warm-up. - 30 min at 70 % of heart rate reserve ([(206–0.88 * age) − resting heart rate] * 0.7 + resting heart rate). - 5 min of cool down.	Usual cancer care	1 day (1)	✓	✓	×	×	1b
Kirkham et al. [57] (2019)	QES	68	During oncology treatment, sessions of 20–30 min of: - Moderate-to vigorous-intensity: 50 %–75 % of heart rate reserve/one repetition maximum) aerobic	–	During oncology treatment: 5 months (60 supervised +20–40 unsupervised). After oncology treatment: 2.5 months (20 supervised +30	×	✓	✓	✓	2c

(*continued on next page*)

Table 1 (*continued*)

Authors	Design	Sample size	Intervention		Time of intervention (number of sessions)	Oncology treatment				LE
			Experimental group	Control group		S	CH	R	ET	
			- Whole-body resistance exercise. After oncology treatment: - Aerobic intervals (4 × [4 min at 75 %–85 % + 4 min at 40 %–65 % VO_2/heart rate reserve]) - Continuous-intensity exercise. Sessions of 20–30 min: - Treadmill, elliptical, or cycle ergometer aerobic exercise at 50–75 % of age-predicted heart rate reserve with progressions every 1–2 weeks as tolerated. - Moderate-intensity, whole body resistance exercises.		unsupervised). Then, 2.5 months (10 supervised +40 unsupervised)					
Kirkham et al. [36] (2020)	CT	37		Usual cancer care	*Not described* (3 sessions/week during CH)	×	✓	×	×	2b
Koelwyn et al. [37] (2016)	CT	60	Incremental cardiopulmonary exercise at 25 %, 50 % and 75 % maximum aerobic power.	Usual cancer care	1 day (1)	✓	✓	✓	✓	2b
Lahart et al. [50] (2018)	RCT	32	Home-based physical activity intervention: Participants received a 30–45 min face-to-face consultation, followed by a support telephone call at the end of months 1, 2 and 3. During each of the last two months (4th and 5th) patients received a mailed physical activity reminder leaflet encouraging their participation.	Usual cancer care	6 months *(not described)*	✓	✓	✓	✓	1b
de Luca et al. [51] (2016)	RCT	20	Supervised sessions of 90-min: - 10 min warm-up (cycle-ergometer pedaling at very light workloads and stretching exercises). - 40 min of resistance training (5 exercises; 2 series of 8 repetitions with a load of 40–60 % of 1 Repetition Maximum). - 30 min of and aerobic training (stationary bike pedaling at 70–80 % of the estimated maximal heart rate). - 10 min cool-down (cycle-ergometer pedaling at very light workloads and stretching exercises).	Usual cancer care	6 months (24)	✓	✓	✓	✓	1b
Naaktgeboren et al. [40] (2022)	CHS	559	Activities carried out at work (i.e., best described as “sedentary,” “standing,” “manual,” or “heavy manual”). For recreational activities, the total hours per week spent on walking, cycling, sports, and gardening were recorded for summer and winter separately to limit seasonal influences.	–	12 months (––)	✓	✓	✓	✓	4
Naaktgeboren et al. [56] (2023)	RCT	185	60-min exercise classes included a warming-up (5 min), aerobic and muscle strength training (25 min each), and a cooling down (5 min). Aerobic training: interval training with a heart rate at (3 × 2 min increasing to 2 × 7 min) or below (3 × 4 min decreasing to 1 × 7 min) ventilatory threshold. Muscle strength: from 2 × 10 repetitions (65 % one-repetition maximum) to 1 × 10 repetitions (75 % one-repetition maximum) and 1 × 20 repetitions (45 % one-repetition maximum).	Usual cancer care	5 months ()	✓	✓	✓	✓	1b
Nagy et al. [34] (2017)	CT	55	Intensive exercise program lasting at least 30 min each session including any individual or team sports.	Usual cancer care	2 years (416–520)	×	✓	×	×	2b
Natalucci et al. [52] (2021) Natalucci et al. [53] (2023)	RCT	30	Lifestyle (nutrition and exercise) educational counseling: in the 15 days prior to the start of the intervention phase, motivational interviews were organized, structured in meetings lasting about one hour. Aerobic training from 40 % to 70 % of heart rate reserve of intensity and from 20 to 60 min of duration.	Lifestyle (nutrition and exercise) educational counseling	3 months (24 sessions remotely supervised +12 on-site supervised)	✓	✓	✓	✓	1b
Naumann et al. [54] (2012)	RCT	50	Group 1: exercise only Group 2: counseling only Group 3: exercise and counseling Exercise program: individualized sessions	Usual cancer care	2 months (24)	✓	✓	✓	✓	1b

(*continued on next page*)

Table 1 (*continued*)

Authors	Design	Sample size	Intervention		Time of intervention (number of sessions)	Oncology treatment				LE
			Experimental group	Control group		S	CH	R	ET	
Nuri et al. [55] (2012)	RCT	29	of 45–60 min. The target goal was 150 min per week of moderate-intensity physical activity including cardiovascular training, strength training, patient-specific rehabilitation, core training, and flexibility Counseling: 1 h session once a week about having cancer and the implications, stress, distress, uncertainty, fear and anxiety, body image, family relationships, intimacy, hopefulness, and future focus Supervised walking program: 45–65 % target heart rate for 25–45 min. Resistance training: sessions of 60 min with 3 sets of 10–14 repetitions each of 9 common exercises.	Supervised walking program	4 months (10 walking sessions +32 resistance sessions)	✓	✓	✓	✓	1b
Stefani et al. [33] (2015)	CT	91	Sessions of 2 h: - 10 min of moderate aerobic exercise. - 90 min of practice in the boat. - 20 min of cool down and stretch	Different sports (3 sessions/ week)	48 months (416)	✓	✓	✓	✓	2b
Toohey et al. [45] (2020)	RCT	16	Sessions of 20–30 min: - Continuous aerobic training group cycled for 30 min: 20 min of them at 55–65 % of their maximal power. - High-intensity interval training group completed seven 30 s intervals (as hard as they could) with 2 min of active recovery between each. Participants were instructed to increase their cadence to between 95 and 115 repetitions per minute to ensure consistent performance.	Usual cancer care	3 months (36)	✓	✓	✓	×	1b
Upshaw et al. [58] (2020)	QES	603	Moderate-strenuous activity summary score of 24 MET or greater, which approximates the recommendation of at least 150 min of moderate-strenuous physical activity per week.	–	1–1.5 months (*variable*)	×	✓	✓	×	2c
Uth et al. [42] (2020)	RCT	68	Football Fitness training: - 10–15-min of warm-up - 15 min of pair- or group-based football drills (passing, dribbling, shooting) and 3–4 × 7 min of small-sided games (4-a-side and 5-a-side) on a 15-m wide, 20-m long pitch with 2-min breaks between matches.	Usual cancer care	12 months (104)	✓	✓	✓	✓	1b
Vincent et al. [59] (2013)	QES	39	Home-based walking training program: sessions of 30 min of aerobic exercise combined with outdoor walking sessions of 15–60 min-long (50–60 % of maximum heart rate).	–	3 months (24)	×	✓	×	×	2c

S: Surgery; CH: Chemotherapy; R: Radiotherapy; ET: Endocrine therapy; LE: Level of evidence; RCT: Randomized controlled trial; CT: Controlled trial; QES: Quasi-Experimental study; —: not applicable; CHS: Cohort study

ejection fraction score in the physical activity group as compared to the control group with MD = 3.21 (95 % CI = −2.03 to 8.45; $p = 0.23$; $I^2 = 84$ %). The forest plot can be seen in Fig. 2A. The other three studies [34,36,38] were non-randomized controlled studies. The results indicated a non-statistically significant change in left ventricular ejection fraction score in the physical activity group as compared to the control group with MD = −1.53 (95 % CI = −3.95 to 0.88; $p = 0.211$; $I^2 = 58$ %). The forest plot can be seen in Fig. 2B.

3.4. Effects of global longitudinal strain

Four studies [36,38,44,56] analysing the variable global longitudinal strain were included in the meta-analysis with a total sample size of 342 participants, all of them completed treatment. Two of them were randomized controlled studies [44,56] (but one of them applied two different interventions to two independent experimental groups [56]). The results did not indicate a statistically significant change in the global longitudinal strain score in the physical activity group as compared to the control group with MD = −0.53 (95 % CI = −1.19 to 0.12; $p = 0.112$; $I^2 = 0$ %). The forest plot can be seen in Fig. 3A. The other two studies [36,38] were non-randomized controlled studies. The results indicated a non-statistically significant change in the global longitudinal strain score in the physical activity group as compared to the control group with MD = −1.57 (95 % CI = −1.28 to 0.97; $p = 0.785$; $I^2 = 0$ %). The forest plot can be seen in Fig. 3B.

3.5. Effects of E/A waveforms ratio

Five articles [34,36,38,44,47] analysing the variable E/A waveforms ratio were included in the meta-analysis with a total sample size of 173 participants all of them completed treatment. Two of them were randomized controlled studies [44,47]. The results did not indicate a statistically significant change in the E/A waveforms ratio score in the physical activity group as compared to the control group with MD = 0.09 (95 % CI = −0.06 to 0.24; $p = 0.245$; $I^2 = 0$ %). The forest plot can be seen in Fig. 4A. The other three studies [34,36,38] were non-randomized controlled studies. The results indicated a non-statistically significant change in E/A waveforms ratio score in the physical

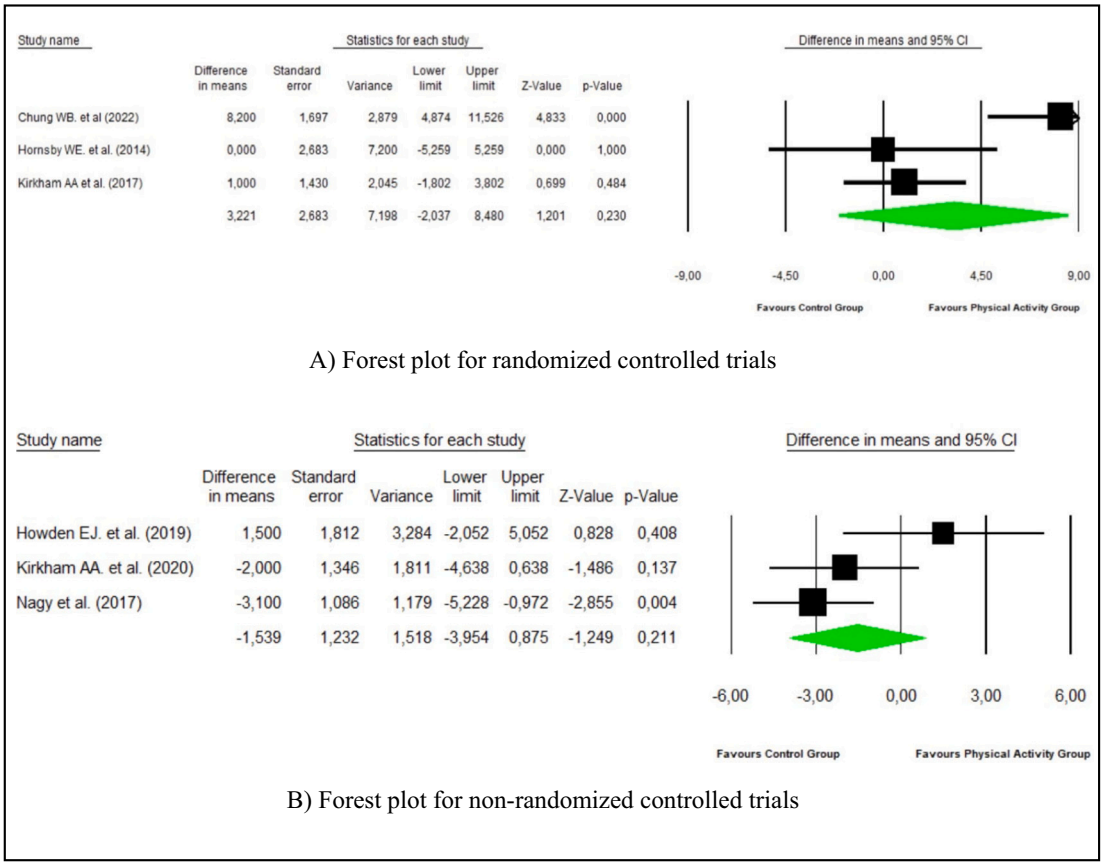


Fig. 2. Forest plots for left ventricular ejection.

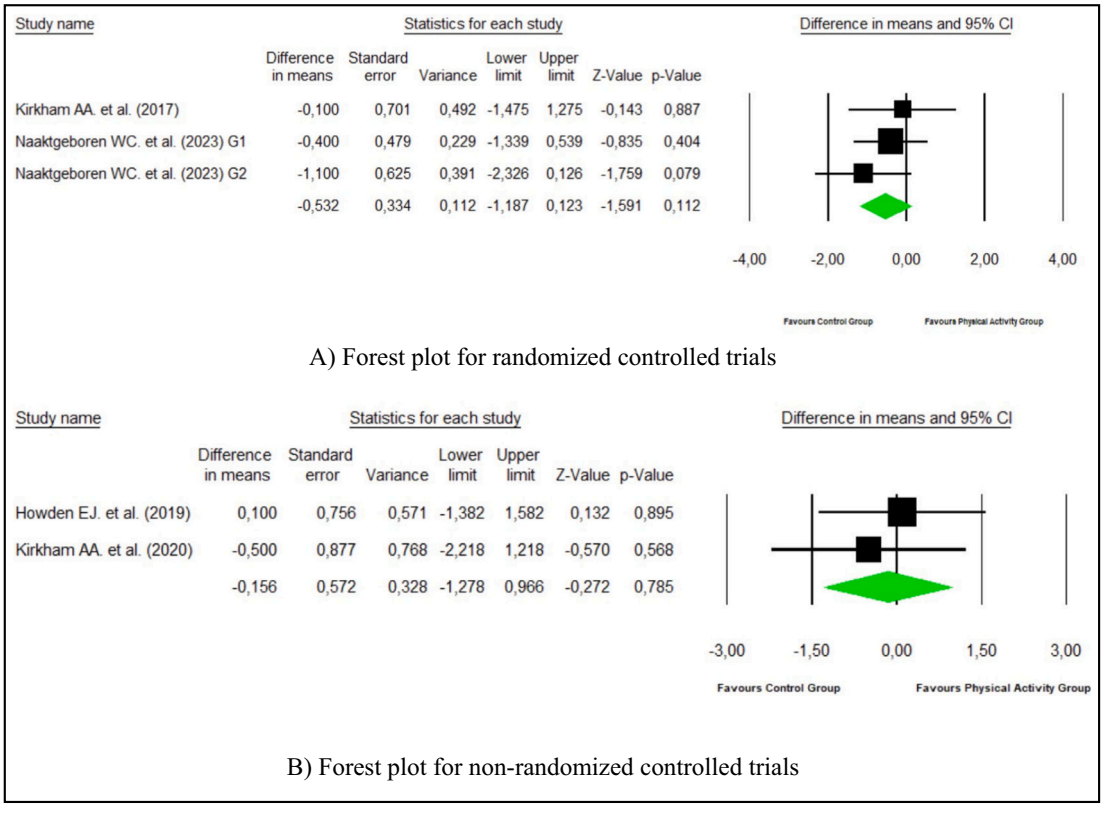


Fig. 3. Forest plots for global longitudinal strain.

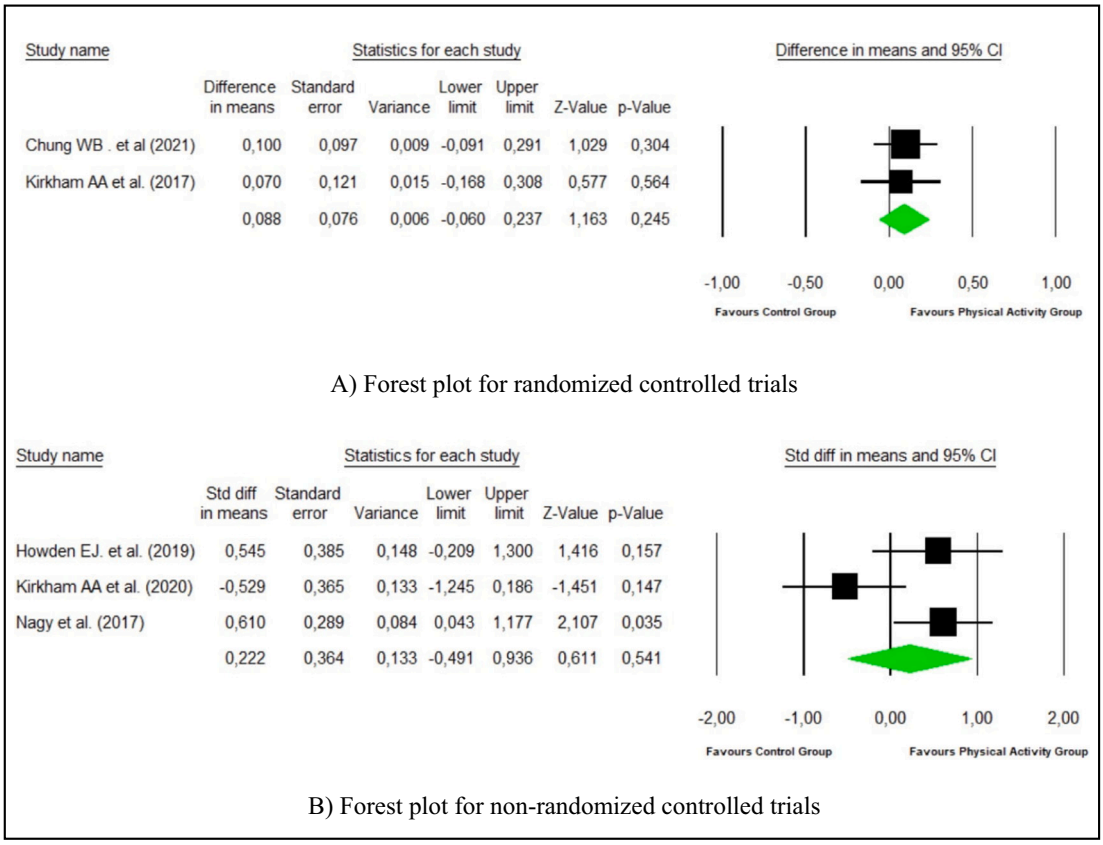


Fig. 4. Forest plots for E/A waveforms ratio.

activity group as compared to the control group with MD = 0.22 (95 % CI = −0.49 to 0.94; $p = 0.541$; $I^2 = 70$ %). The forest plot can be seen in Fig. 4B.

3.6. Effects of VO_2max

Twelve studies [32,35,38,42,45,47–51,55,56] analysing the variable VO_2max were included in the meta-analysis with a total sample size of 680 participants VO_2max. Ten of them were randomized controlled studies [42,45,47–51,55,56]. Analysis was divided into two subgroups: finished treatment versus unfinished treatment. Analysis in the first subgroup consisting of two studies [47,51] indicated no statistically significant improvement in VO_2max score in the physical activity group than in the control group with MD = 1.43 (95 % CI = −0.93 to 3.78; $p = 0.234$; $I^2 = 79$ %). Also, analysis in the second subgroup indicated a statistically significantly improve in VO_2max score in the physical activity group than control group with MD = 3.07 (95 % CI = 1.24 to 4.89; $p = 0.001$; $I^2 = 78$ %). Finally, the results indicated a statistically significantly improve in VO_2max score in the overall physical activity group than control group with MD = 2.45 (95 % CI =1.01 to 3.89; p = 0.001; $I^2 = 76$ %) (Fig. 5A).

The other three studies are non-randomized controlled studies [32,35,38], all of them completed treatment. The results indicate a statistically significant change in VO_2max score in the physical activity group as compared to the control group with MD = 4.62 (95 % CI = 2.47 to 6.78; $p < 0.001$; $I^2 = 80$ %). The forest plot can be seen in Fig. 5B.

3.7. Risk of bias for individual studies

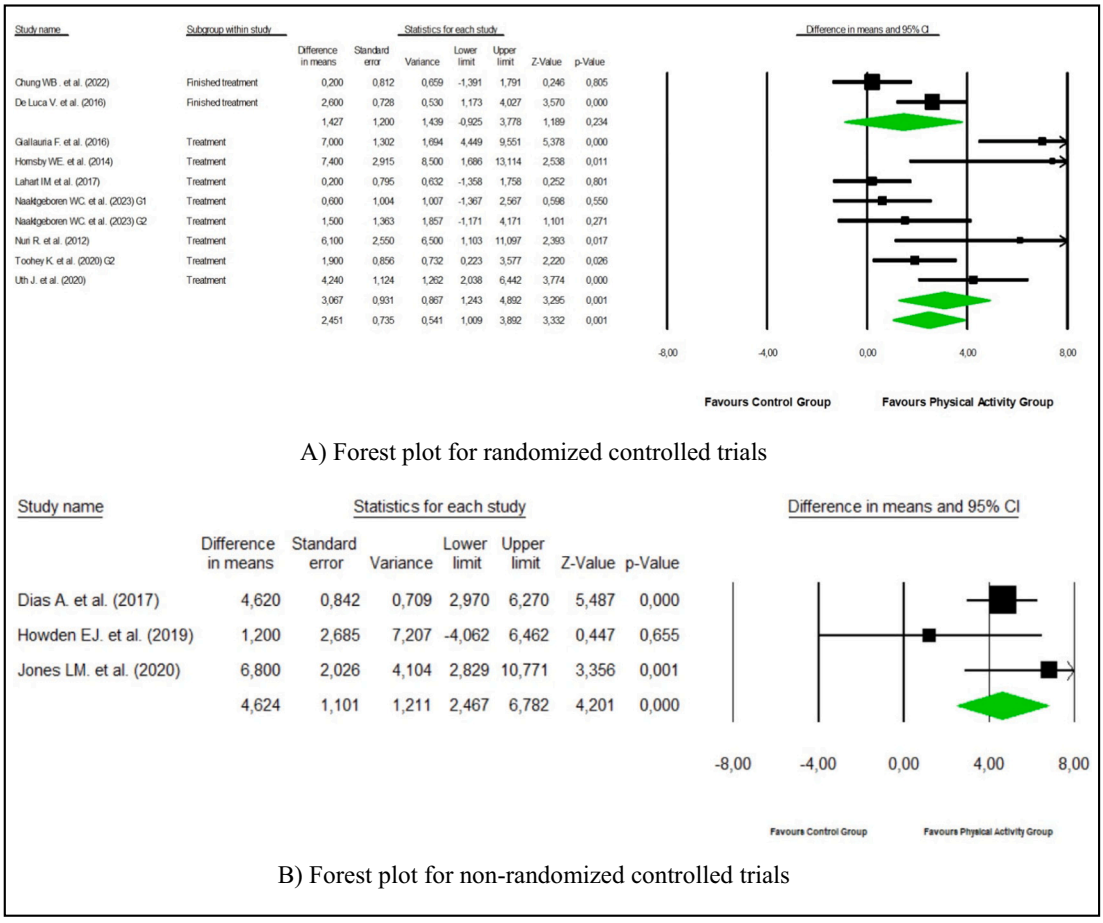
The risk of bias within individual studies was determined to be critical in 18 studies (64.3 %) [32,33,35,39–41,46,48,50–59] while eight studies had a low risk of bias (28.6 %) [34,37,38,42–45,49] (Tables 2 & 3).

Additionally, the certainty of the evidence obtained was assessed as moderate for the variables of ventricular ejection fraction, E/A waveforms ratio and VO_2max and high for the global longitudinal strain (Table 4).

4. Discussion

The American College of Sports Medicine endorsed that exercise is able to mitigate many of the symptoms derived from the cardiotoxicity of cancer treatments [14]. However, it has not been specified which signs or symptoms resulting from cardiotoxicity can be preserved by the implementation of physical activity programs. Hence, the aim of this work was to analyze the cardioprotective effect of exercise in women who are receiving and/or have completed their BC treatments. The systematic review and meta-analysis performed have shown that the effects of exercise on left ventricular ejection fraction, global longitudinal strain and E/A waveforms ratio are non-significant. However, its effect on VO_2max is significant, especially if performed during oncological treatment.

In fact, this is one of the most analyzed variables in the included studies [32,35–42,45–56,59], probably because of its intimate relationship with the cardiovascular system and its representation of the functional capacity of the patients. According to the Fitness Registry and the Importance of Exercise National Database, all patients started with normal values according to their age [60], except in one study [43]. However, even starting from normal values, significant improvements were observed [32,35,38,39,41,45,46,48,49,51–55,59]. This should be taken into account since this parameter is a predictor of death from any cause, especially cardiovascular disease [36,61,62]. A previous meta-analysis concluded that exercise during cancer treatment should be aimed at maintaining VO_2max and reducing associated symptoms [63].



A) Forest plot for randomized controlled trials

B) Forest plot for non-randomized controlled trials

Fig. 5. Forest plots for VO_2max.

Table 2
Risk of bias for non-randomized included studies (ROBINS-I tool results).

Authors	Confounding[a]	Selection[b]	Classification of interventions	Derivation from intended intervention	Missing data[c]	Outcomes	Selective reporting[d]	Overall
Dias et al. [35] (2017)	Critical	Low	Critical	Low	Low	Low	Low	**Critical**
Foulkes et al. [39] (2019)	Moderate	Critical	Low	Low	Low	Low	Low	**Critical**
Howden et al. [38] (2019)	Moderate	Low	Low	Low	Low	Low	Low	**Low**
Jones et al. [32] (2020)	Critical	Low	Critical	Low	Low	Low	Low	**Critical**
Kirkham et al. [57] (2019)	Critical	Low	Critical	Low	Low	Low	Low	**Critical**
Kirkham et al. [36] (2020)	Moderate	Low	Moderate	Low	Low	Low	Low	**Moderate**
Koelwyn et al. [37] (2016)	Moderate	Low	Low	Low	Low	Low	Low	**Low**
Naaktgeboren et al. [40] (2022)	Critical	Moderate	Critical	Critical	Low	Low	Low	**Critical**
Nagy et al. [34] (2017)	Moderate	Low	Low	Low	Low	Low	Low	**Low**
Stefani et al. [33] (2015)	Critical	Low	Low	Low	Low	Low	Low	**Critical**
Upshaw et al. [58] (2020)	Critical	Low	Critical	Low	Low	Low	Low	**Critical**
Vincent et al. [59] (2013)	Critical	Low	Critical	Low	Low	Low	Low	**Critical**

[a] Risk of bias from confounding was considered critical when confounding was not inherently controlled for (i.e. no or limited adjustment).
[b] Selection bias was critical when selection into the study was very strongly related to intervention and outcome. This occurred when the study included women with diagnoses other than breast cancer.
[c] Risk of bias due to missing data was considered moderate when there appeared to be a substantial amount of missing data. In these cases, the proportions of and reasons for missing data might differ across interventions groups. Of note, the majority of studies did not report on missing data. The risk of bias for these were classified as low, but could also be considered "unknown".
[d] The studies with a moderate risk for selective outcome reporting were those that did not provided a pre-registered protocol.

Table 3
Risk of bias for randomized included studies (RoB tool results).

Authors	Random sequence (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall
Arem et al. [41] (2016)	Low	Critical	Critical	Critical	Critical	Low	Low	**Critical**
Casla et al. [46] (2015)	Low	Critical	Critical	Critical	Low	Low	Low	**Critical**
Chung et al. [47] (2022)	Low	Low	Moderate	Low	Moderate	Low	Low	**Moderate**
Giallauria et al. [48] (2016)	Low	Low	Critical	Critical	Low	Low	Low	**Critical**
Hornsby et al. [49] (2014)	Low	Low	Moderate	Low	Low	Low	Low	**Low**
Kirkham et al. [44] (2017)	Low	Low	Moderate	Low	Low	Low	Low	**Low**
Kirkham et al. [43] (2018)	Low	Low	Moderate	Low	Low	Low	Low	**Low**
Lahart et al. [50] (2018)	Low	Low	Critical	Critical	Low	Low	Low	**Critical**
de Luca et al. [51] (2016)	Low	Low	Critical	Critical	Low	Low	Low	**Critical**
Naaktgeboren et al. [56] (2023)	Low	Low	Critical	Critical	Low	Low	Low	**Critical**
Natalucci et al. [52] (2021) Natalucci et al. [53] (2023)	Low	Critical	Critical	Critical	Low	Low	Low	**Critical**
Naumann et al. [54] (2012)	Low	Critical	Critical	Critical	Low	Low	Low	**Critical**
Nuri et al. [55] (2012)	Low	Critical	Moderate	Low	Low	Low	Low	**Critical**
Toohey et al. [45] (2020)	Low	Low	Moderate	Low	Low	Low	Low	**Low**
Uth et al. [42] (2020)	Low	Low	Moderate	Low	Low	Low	Low	**Low**

[a]Risk of bias from confounding was considered critical when confounding was not inherently controlled for (i.e. no or limited adjustment).
[b]Selection bias was critical when selection into the study was very strongly related to intervention and outcome. This occurred when the study included women with diagnoses other than breast cancer.
[c]Risk of bias due to missing data was considered moderate when there appeared to be a substantial amount of missing data. In these cases, the proportions of and reasons for missing data might differ across interventions groups. Of note, the majority of studies did not report on missing data. The risk of bias for these were classified as low, but could also be considered "unknown".
[d]The studies with a moderate risk for selective outcome reporting were those that did not provided a pre-registered protocol.

Table 4
Certainty of the evidence (GRADE).

Outcomes	Number of participants (studies)	Risk of bias[a]	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of the evidence (GRADE)
VO_2max	549 (9 RCT)	Critical	Moderate[b]	Low	Low	None	⨁⨁⨁◯ Moderate
Left ventricular ejection fraction	195 (3 RCT)	Low	Moderate[b]	Moderate	Low	None	⨁⨁⨁◯ Moderate
Global longitudinal strain	274 (2 RCT)	Low	Low	Low	Low	None	⨁⨁⨁⨁ High
E/A waveforms	176 (2 RCT)	Moderate	Moderate[b]	Moderate	Low	None	⨁⨁⨁◯ Moderate

RCT: randomized clinical trial; SMD: standardized mean difference.
[a] The average risk of bias of the studies according to the ROBINS-I and RoB tools.
[b] Low methodological heterogeneity but high statistical heterogeneity among trials ($I^2 > 25$ %).

However, exercise after treatment should aim to increase VO_2max [63]. These previous findings are congruent with those identified in this review and meta-analysis. Although Dias et al. [35] noted an improvement in the exercise group in the treatment period (which could be due to the sample starting the study with very low VO_2max levels) and Uth et al. [42] did not identify any change (most likely due to low adherence to their intervention).

Systolic function was analyzed through left ventricular ejection fraction and global longitudinal strain. In fact, left ventricular ejection fraction was the most studied parameter [36–38,40,43,44,47,56,58]. However, in no case were significant changes identified in any of the variables associated with systolic function. In parallel, Kirkham et al. [44] observed that 24 h after chemotherapy, in the control group, left ventricular ejection fraction was preserved (59 %) and troponin T was maintained, but systemic vascular resistance fell. This could be due to an increase in N-terminal pro-brain natriuretic peptide [43,64]. The latter and troponin T are released into the bloodstream in the presence of cardiac damage and have been proposed as possible prognostic

indicators of cardiotoxicity [64–66]. The same changes were observed in the exercise group, except for N-terminal pro-brain natriuretic peptide, which remained well below the control group [43]. Thus, exercise could produce an immediate effect on endothelial function between 12 and 24 h after exercise, inducing vasodilation [67] and the release of N-terminal pro-brain natriuretic peptide to maintain homeostasis [64]. Thus, exercise practiced 24 h before chemotherapy administration could have a cardioprotective effect. However, when Kirkham et al. [43] performed the assessments 14 days later, the control group remained at values approximating the previous measurement (further decreasing systemic vascular resistance) while an unexpected increase in N-terminal pro-brain natriuretic peptide was observed in the exercise group. Therefore, these findings seem to indicate that the vasodilatory effects of exercise disappear after 48 h and a cumulative effect could only be achieved if practiced continuously [64]. Thus, the loss of vasodilatation could explain the increase in N-terminal brain natriuretic propeptide in the exercise group. For its part, global longitudinal strain measures the degree of deformation experienced by myocardial fibers between systole and diastole in the longitudinal axis. Although no significant changes were identified in any case, we could be facing the same situation as with the left ventricular ejection fraction and it is possible that the time factor is a determining factor in the behavior of this variable.

Independently, (non-significant) changes in left ventricular ejection fraction were identified during exercise from low intensities (25 % of VO_2max) [37,38]. It should be taken into account that it is normal during exercise for the left ventricular ejection fraction to increase. However, what is observed in these cases is an imbalance between end-diastolic and end-systolic volume. According to the Frank-Starling law [68], the myocardium has the ability to adapt to blood volumes; thus, when the diastolic volume increases (e.g., during exercise due to increased metabolic demand), the systolic volume will also increase. In these articles [37,38], although the diastolic volume increases, the same does not occur with the systolic volume, thus indicating a possible dysfunction in myocardial contractility that is only detected during exercise. In addition, the significant variation in measurement techniques employed for left ventricular ejection fraction assessments (2DE, 3DE, and cardiac magnetic resonance imaging), coupled with the inherent constraints associated with each method (image quality, operator proficiency, variability in repeated measures), might have introduced intricacies in deciphering the data.

Diastolic dysfunction was assessed by echocardiographic parameters such as the E/A waveforms ratio (i.e., the ratio between the E wave or early diastolic filling velocity and the A wave or late diastolic filling velocity). An increase in this parameter and cardiac output was detected 24 h after chemotherapy [38,44]. Considering that preload is highly influenced by cardiac output (as well as left ventricular ejection fraction and global longitudinal strain) [69], the E/A waveforms ratio could also be increased. In the assessments two weeks later, stabilization was observed in the exercise group; this was not the case in the control group, which, despite continuing with an increase in cardiac output, experienced a decrease in the E/A waveforms ratio [36,43].

Although this meta-analysis has reported some novel findings, we note several limitations. The main limitations of the present review are the great heterogeneity of the included studies and the small proportion of clinical trials. Similarly, the great plurality in the variables analyzed, the small sample size and the lack of detail in some articles reduce the generalizability of the results obtained. The lack of detail in the oncological treatments administered and the publication bias due to the fact that four studies belong to the same group of investigators also affect the generalizability of the results obtained.

Therefore, systemic therapies have a strong implication on the functional capacity of patients, which is also associated with other symptomatology such as fatigue, depression or decreased quality of life, for which there is strong scientific evidence of the efficacy of a 12-week program of aerobic training combined with resistance [58,65]. Future lines of research should consider carrying out a follow-up with a period longer than 5 years, taking into account that mortality rates increase exponentially after this time. In addition, these should also consider the study of functional capacity, due to the close relationship with other symptoms associated with these treatments and the fact that VO_2max can be used to predict cardiovascular risk.

5. Conclusions

Exercise does not seem to be effective in avoiding the cardiotoxic effects of oncological treatment for breast cancer. Specifically, it does not improve left ventricular ejection fraction, global longitudinal strain and E/A waveforms ratio in a significant way. However, its effect on VO_2max is significant, especially if performed during oncological treatment.

However, its ability to improve pressures, cardiac output, stroke volume and systemic vascular resistance, even with mismatched values of hemoglobin, hematocrit, N-terminal pro-brain natriuretic peptide and troponins, does not allow us to rule out the possible cardioprotective effect of exercise (especially in chemotherapy treatment).

Therefore, more clinical trials should be carried out always taking into account the doses of the treatments administered and the measurements of both heart rate variability and pulse wave velocity in an integrated manner, because of their intimate relationship with these treatments. However, due to the limitations of this meta-analysis (few included studies and poor stability of combined results), more high-quality and large-sample randomized controlled trials for verification are recommended.

Contributors

Alicia Fernández-Casas conceptualized and designed the study, drafted the initial manuscript, designed the data collection instruments, collected data, carried out the initial analyses, and critically reviewed the manuscript for important intellectual content.

Raquel Leirós-Rodríguez conceptualized and designed the study, drafted the initial manuscript, designed the data collection instruments, collected data, carried out the initial analyses, and critically reviewed the manuscript for important intellectual content.

Pablo Hernandez-Lucas conceptualized and designed the study, drafted the initial manuscript, designed the data collection instruments, collected data, carried out the initial analyses, and critically reviewed the manuscript for important intellectual content.

Alicia González-Represas conceptualized and designed the study, drafted the initial manuscript, designed the data collection instruments, collected data, carried out the initial analyses, and critically reviewed the manuscript for important intellectual content.

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The authors declare that they have no competing interest.

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