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Recreational physical activity reduces breast cancer recurrence in female survivors of breast cancer: A meta-analysis

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ABSTRACT

Purpose: The aim of this review was to systematically collect the published evidence to assess the effect of recreational physical activity (PA) in reducing breast cancer (BC) recurrence in female survivors.
Methods: A bibliographic search was carried out in PubMed Medline, CINAHL Complete, Scopus and Lilacs until June 2021. We selected observational studies or clinical trials comprising women diagnosed with BC, in which the risk of recurrence of BC was measured before or after performing recreational PA. As a secondary outcome, we analyzed disease free survival for recurrence/disease-specific mortality. The methodological quality of observational studies was assessed with the Newcastle-Ottawa Scale and clinical trials with the PEDro scale. A random effects model was used to estimate the relative risks (RR) and their 95% confidence intervals (CI) to infer the results for any female survivor of BC. We performed separate meta-analyses for prediagnosis and postdiagnosis recreational PA.
Results: Eleven studies were included, providing data from 29,677 surviving women with BC with an age range of 18–79 years old. Postdiagnosis recreational PA reduced the risk of BC recurrence by 16% (RR, 0.84; 95% CI: 0.78 to 0.91) and the risk of recurrence/disease-specific mortality by 23% (RR, 0.77; 95% CI: 0.66 to 0.93). Prediagnosis PA reduced the risk of BC by 18% (RR, 0.82; 95% CI: 0.74 to 0.91).
Conclusion: This systematic review with meta-analysis shows that recreational PA can be an interesting therapeutic tool to protect against recurrence of BC in female survivors.

1. Introduction

Breast cancer (BC) is the most commonly diagnosed neoplasm in women worldwide (Ahmad, 2019). BC represents a quarter of all cancers diagnosed in women (Ferlay et al., 2015), affecting 2.1 million women each year, and its incidence varies widely, ranging from 27/100,000 (Central-East Asia and Africa) to 85–94/100,000 (Australia, North America and Western Europe) (Sancho-Garnier and Colonna, 2019). Although deaths related to BC are large in women (currently, approximately 15% of all cancer deaths among women), the BC survival rates have increased significantly in recent decades (Saadatmand et al., 2015), motivated especially by the development of new surgical, genetic, pharmacological and conservative therapeutic approaches. Besides, the disease free survival (DFS) (recurrence/disease-specific mortality) rate at 5 years is greater than 80% (Strasser-Weippl and Goss, 2013).

Low levels of physical activity (PA) may be considered a risk factor for developing BC (Chong et al., 2021) increasing the risk of BC 15.5% in sedentary works (Lee et al., 2021). To combat this unhealthy behavior, several studies have described that practice regular PA is a protective factor for BC (Marzo-Castillejo et al., 2020). Generalized PA includes a wide variety of sport-dependent exercises or exercises that may require a great deal of effort due to their intensity. One of the most appropriate ways to perform PA in a playful, constant way and that could achieve greater adherence is recreational PA. Recreational PA involves the practice of exercises derived from sports, fitness or relaxation activities such as Tai Chi, yoga, dance or mindfulness, among others (Pazmino et al., 2021), carried out in a relaxed manner and with adequate breaks

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(Holtermann et al., 2018). Recreational PA are those that are not oriented to domestic, occupational or sports performance work that include repetitive and fast tasks within a controlled environment and that often do not have enough rest or recovery time (work activity) (Pazmino et al., 2021). Recreational PA includes ludic exercise that can be performed with low or moderate intensity, allowing sports practice to be adapted to the physical state of the patients.

The increase of BC surviving women also favors the recurrence of BC, estimating between 9% and 47% (Engelhardt et al., 2014). Recreational PA could be an interesting therapy to reduce the BC recurrence. Some reviews have tried to analyze the effect of PA to reduce the BC recurrence in women survivors (Friedenreich et al., 2016; Lahart et al., 2015; Spei et al., 2019) However, their findings are not conclusive due to thelow number of included studies, the inconsistency of the findings (Friedenreich et al. and Lahart et al. found a protective effect whereas Spei et al. found no effect), the absence of quality assessment of the include studies (Friedenreich et al., 2016) or the heterogeneity of the meta-analysis results (Spei et al., 2019). To date, there are no adequately powered meta-analysis that have evaluated the impact of pre diagnosis and postdiagnosis recreational PA in BC recurrence. Thus, the aim of this study was to collect systematically all published evidence to assess the effect of pre and postdiagnosis recreational PA in BC recurrence.

2. Methods

2.1. Design

The *2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement (Page et al., 2021) and the 2nd Edition of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Thomas, 2020) were followed to performed the meta-analyses and report the findings. In addition, the present review was previously registered in the PROSPERO (CRD42020221298). Each phase of this review was performed by two authors, independently, and disagreements were resolved by a third author.

2.2. Search strategy and data sources

A bibliographic search of 4 international databases (PubMed MEDLINE, CINAHL Complete, Scopus, and Lilacs) was performed up to June 2021 by two authors, independently. In addition, we consulted the reference lists from retrieved full-text studies, previous reviews and grey literature to collect possible potential references. A highly sensitive strategy was designed using the following keyword contents in PubMed and CINAHL Thesaurus (*Medical Subjects Headings* [MeSH] and *CINAHL Headings*, respectively). Therefore, the keywords "exercise", "physical activity", "recurrence" and "breast cancer" were combined in different search conditions using the Boolean operators "and"/"or". No publication date or language filters were set. Table 1 displays the search strategy used in each database.

2.3. Study selection

Two reviewers, independently, screened the titles and abstracts of all studies retrieved in the preliminary search. When one of the authors selected an article in this phase, it was examined in detail. Disagreements that arose during full-text screening were resolved by reference to a third reviewer.

To be included in the review, a study must meet all of the following inclusion criteria, based on the components of PICOS (Population, Intervention, Comparison, Outcomes and Study design): 1) longitudinal observational studies or clinical trials with a control group; 2) whose study population was women diagnosed with BC; 3) in which the relationship between recreational PA (intervention/exposure) and recurrence (outcome) was measured, with recreational PA and recurrence measured independently without linking to another factor/result; and 4) with statistical data that can be included in a meta-analysis.

Table 1
Search Strategy in each Database.

DATABASES	SEARCH STRATEGY
PubMed Medline	(exercise* OR physical activit*) AND (recurrence) AND (breast neoplasm* OR breast cancer*)
CINAHL	(exercise* OR physical activit*) AND (recurrence) AND (breast neoplasm* OR breast cancer*)
SCOPUS	(INDEXTERMS("exercise") OR TITLE-ABS-KEY (physical activit*)) AND INDEXTERMS("recurrence") AND (INDEXTERMS ("breast neoplasms") OR TITLE-ABS-KEY (breast cancer*))
LILACS	(Actividad física OR ejercicio físico) AND cáncer de mama

2.4. Data extraction

Data were extracted using a standardized Microsoft Excel data-collection form by two authors, independently. Data extracted from each selected study were authorship and publication date, study design, sample characteristics of the experimental and control groups (sample size, age and time since BC diagnosis), and characteristics of the recreational PA (type, intensity, prediagnosis or postdiagnosis assessment). In addition, data necessary to estimate the effect size (events of recurrence) were extracted from each study. Due to the similarity between recurrence and DFS, we extracted data of DFS events (recurrence/disease-specific mortality) in revised studies as a secondary outcome.

2.5. Quality assessment

To assess the quality of the studies included in this review, we used the PEDro Scale (Macedo et al., 2010) for randomized controlled trials (RCTs) and the Newcastle–Ottawa Scale (Wells et al., 2009) for observational studies. Scores of previous scales were transformed proportionally to 10 points for study comparability.

To assess the strength of evidence from this review, we followed the recommendations of the *Grading of Recommendations, Assessment, Development and Evaluation* (GRADE) (Schü;nemann et al., 2017) and the criteria developed by Meader et al. (2014) According to the GRADE system, the quality of the evidence is classified as high, moderate, low or very low. High quality was considered if the included studies were RCTs or low quality if they were observational. In addition, the level of quality was downgraded one position for each of the problems in the included studies related to risk bias, inconsistency in results, indirect evidence, imprecision and publication bias. The risk of bias was rated as "not serious" (if no study or less than half of them had a bias), "serious" (if more than half of the studies had a bias) or "very serious" (if more than half of the studies had two or more biases). Inconsistency was measured by the Cochrane Q and the degree of inconsistency (I^2) (Higgins et al., 2003), which is classified as absent ($I^2 = 0\%$), moderate ($I^2 < 40\%$) or high ($I^2 \geq 40\%$). Indirect evidence exists in those articles in which the results are measured indirectly, qualifying as "yes" or "no". Inaccuracy was assessed based on the number of included studies (high$>$ 10, medium between 5 and 9 and low $<$5) and the average number of people per study (high$>$ 300, medium between 100 and 300 and low $<$100). Finally, publication bias was classified as absent, not serious or serious based on the symmetry of the funnel plot, the value of Egger's *p* Test (Egger et al., 1997) (no bias $p > 0.1$) and the percentage variation of the average effect adjusted by the trim and fill method in conditions of absence of publication bias (Duval and Tweedie, 2000). For this last criterion, a 10% variation limit was taken, following Rothman's recommendations for the effect size variation limit in the assessment of confounding bias (Rothman et al., 2008).

2.6. Statistical analysis

Meta-analyses were carried out using Comprehensive Meta-Analysis

version 3.0 (Biostat, Englewood, NJ, USA) (Borenstein et al., 2020). Two authors performed the meta-analyses, independently, and no differences were observed among them. A random effects model was used to estimate the combined effects and their 95% confidence intervals (95% CI) to infer the results from any female survivor of BC(Cooper et al., 2009; DerSimonian and Laird, 1986). Regarding the average effect, it was decided to collect events and calculate the relative risks (RR), since in most studies on the question investigated only measures adjusted for third variables appear (Lahart et al., 2015), and the variation of the third variable from one study to another (Peterson and Brown, 2005). In line with previous studies carried out on this topic, separate meta-analyses were performed for pre-diagnosis and post-diagnosis PA. In studies including more than one group of exposed according to the intensity of recreational PA, each group of exposure was taken into account independently to assess whether the intensity of recreational PA was related to the effect, for what was computed in each study as many independent combinations as exposure groups. In the case of more than one sample in the same study, the sample average was computed.

We conducted sensitivity analyses to determine the robustness of the results (subgroup analyses and leave-one-out analysis). The subgroup analyses were based on design, outcome measure, intensity of recreational PA and level of non-exposure. For intensity analyses, we used the PA Guidelines for Americans (Piercy et al., 2018) (low, moderate or high active). Because the level of exposure of studies does not exactly match with categories in this classification, we classified each exposure level in the category most coincident.

3. Results

3.1. Flow of studies through the review

We found 1271 articles from databases and 2 articles obtained from other sources. After eliminating duplicates, we reviewed 945 articles of which 898 were discarded due to being irrelevant and 35 were discarded due to not meeting the inclusion criteria (reasons in Fig. 1). Only one study did not differentiate between recreational, occupational or domestic PA (Ansa et al., 2015), while only one provided data for the three types of activity (Friedenreich et al., 2009). The rest of the studies measured recreational PA. Therefore, this analysis focused on recreational PA, rejecting the first study and taking into account only the recreational activity data from the second. Thus, 11 studies (Bao et al., 2015; Bertram et al., 2011; Chen et al., 2011; Courneya et al., 2014; Friedenreich et al., 2009; Hayes et al., 2018; Holmes et al., 2005; Jones et al., 2016; Jung et al., 2019; Nechuta et al., 2016; Schmidt et al., 2013) were included for the quantitative synthesis (Fig. 1).

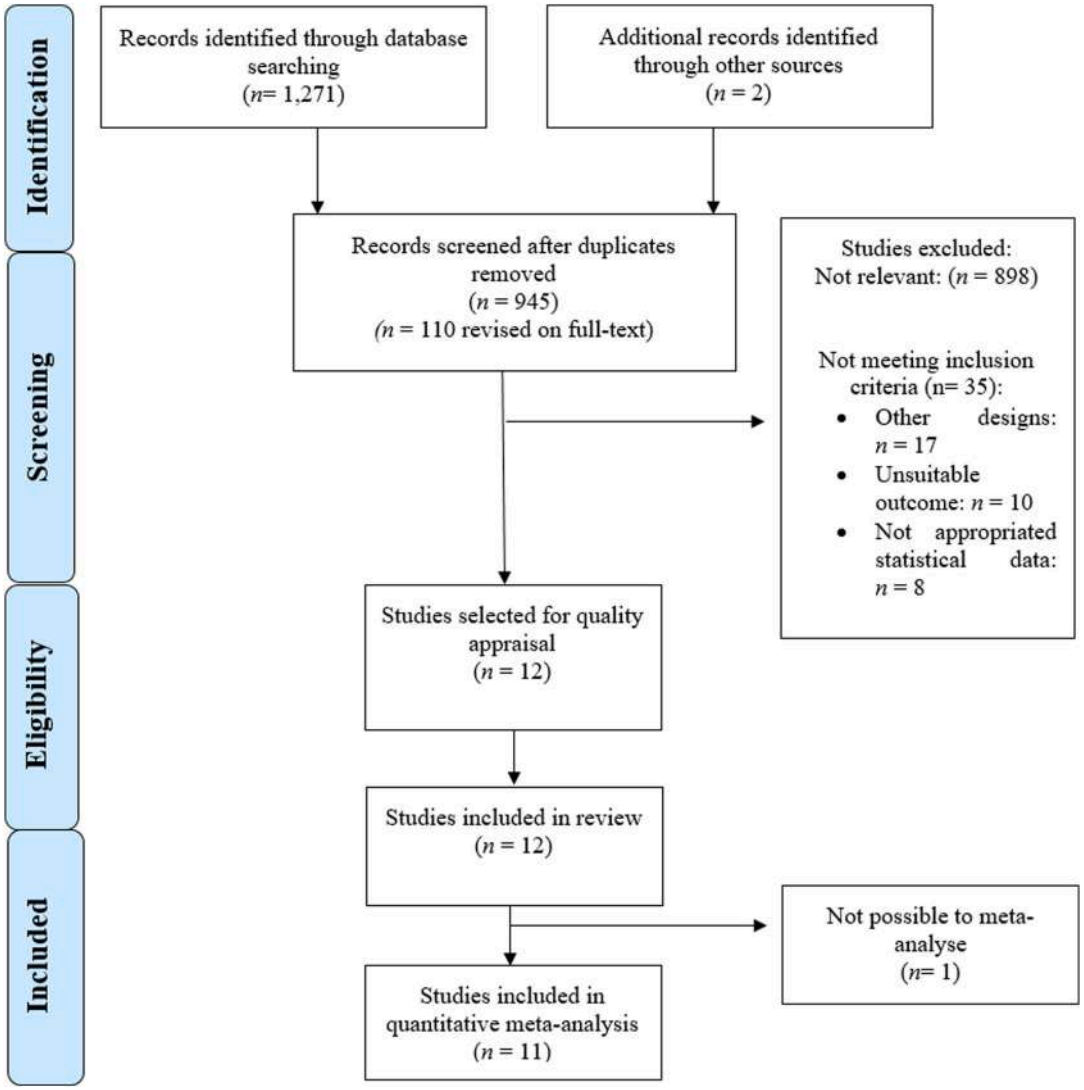

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for the systematic literature search and study selection process.

3.2. Characteristics of studies included

All studies included in the present review were carried out between 2009 and 2019. Nine studies followed an observational study design (Bao et al., 2015; Bertram et al., 2011; Chen et al., 2011; Friedenreich et al., 2009; Holmes et al., 2005; Jones et al., 2016; Jung et al., 2019; Nechuta et al., 2016; Schmidt et al., 2013), and 2 studies were RCTs (Courneya et al., 2014; Hayes et al., 2018). The included studies provided data from 29,677 women diagnosed with BC with an age between 18 and 79 years old. The outcomes measured was recurrence in 9 studies and recurrence/disease-specific mortality in 2. Postdiagnosis recreational PA in BC recurrence was measured in 7 studies and prediagnosis in 3 studies. Studies with recurrence/disease-specific mortality included postdiagosis recreational PA. The characteristics of the included studies are shown in Table 2.

3.3. Methodological quality assessment

The mean methodological score of the included studies was 8.2 ± 1.7 points, which indicates a moderate-high methodological quality of the studies. The methodological quality in the observational studies was higher (8.8 ± 1.3) than of the RCT (5.8 ± 1.2). Supplementary online Table 1 shows the methodological quality of the included studies.

3.4. Postdiagnosis recreational physical activity in breast cancer recurrence

We included 18 independent comparisons from 7 studies (Bertram et al., 2011; Courneya et al., 2014; Hayes et al., 2018; Holmes et al., 2005; Jones et al., 2016; Jung et al., 2019; Nechuta et al., 2016). We found a negative and significant relationship between postdiagnosis recreational PA and recurrence of BC (RR, 0.84; 95% CI: 0.78 to 0.91; n = 20,686; average sample size: 2955.1) (Table 3, Fig. 2). Thus, postdiagnosis PA reduces the risk of BC recurrence by 16%. The methodological quality of the included studies was moderate to high (8 ± 1.6). There was no evidence of heterogeneity (Q, 17.03; degree of freedom [df], 17; p-value for Q, 0.45; I^2, 0.15%). No risk of publication bias was found (p for Egger's test, 0.37 and no variation after trim and fill estimation respect to the original RR) (Supplementary Online Fig. 1).

In the sensitivity analysis, we found no statistically significant differences for design (observational: RR, 0.84; 95% CI: 0.78 to 0.91; experimental: RR, 0.7; 95% CI: 0.4 to 1.21), outcome measure (recurrence: RR, 0.88; 95% CI: 0.79 to 0.98; corrected: RR, 0.81; 95% CI: 0.73 to 0.9), intensity of recreational PA (low-moderate: RR, 0.88; 95% CI: 0.81 to 0.98; high: RR, 0.79; 95% CI: 0.72 to 0.88) or level of non-exposure (no exercise: RR, 0.75; 95% CI: 0.62 to 0.91; very low exercise: RR, 0.86; 95% CI: 0.79 to 0.93). In addition, quantitative meta-regression did not explain any level of heterogeneity according to the quality of the included studies ($p = 0.31$). Leave-one-out analyses did not show substantial variation respect original pooled effect. In addition, we calculated the pooled effect taking into account the mean of the comparisons (levels of exposure) in each study (RR, 0.84; 95% CI: 0.78 to 0.91), which is the same as the initial pooled effect.

Table 2
Characteristics of the studies included in the review.

Authorship and date	Study Design	Assessm Time	Age women	Exposed		Non-Exposed		Outcomes		Methodological Quality		
				Ne	Exposition (MET/ week)	Nne	Exposition (MET/ week)	Detailled	Grouped	Non-adjusted scores	Adjusted score	Quality
Bao et al. (2015)	Prospective Observational	Post Post	20–75 20–75	165 178	<7,6 >7,6	175	No Exercise	DFS (Recurr/ DRBC)	Corrected	NOS (10)	10	High
Bertram et al. (2011)	Prospective Observational	Post Post Post Post	18–70 18–70 18–70 18–70	485 451 472 472	2,5–7,4 7,5–14,9 15,0–24,7 24,8-107	481	<2,5	Recurr/ NPBC	Recurr	NOS (7,8)	7,8	Moderate-High
Chen et al. (2011)	Prospective Observational	Post Post	20–75 20–75	764 760	<8,3 ≥8,3	835	No Exercise	DFS (Recurr/ DRBC)	Corrected	NOS (7,8)	7,8	Moderate-High
Courneya et al. (2014)	RCT	Post	>18	160	>12,0	82	Usual Care	Recurr	Recurr	PEDro (6,7)	6,7	Moderate
Friedenreich el al. 2009	Cohort Study	Pre	<80	303	>19,0	306	<5,0	Recurr	Recurr	NOS (10)	10	High
Hayes et al. (2018)	RCT	Post Post	52,3 52,9	134 73	NR 3,0–8,9	60 70	Usual Care	Recurr/ DRBC	Corrected	PEDro (5)	5	Moderate
Holmes et al. (2005)	Prospective Observational	Post Post Post Post	30–55 30–55 30–55 30–55	862 335 428 403	9,0–14,9 15,0–23,9 >23,9 2,0–10,0	959	<3,0	Recurr/ DRBTWR	Corrected	NOS (8,9)	8,9	High
Jones et al. (2016)	Cohort Study	Post Post Post	18–79 18–79 18–79	1538 1566 1533	10,1-25 >25 <7,5	1554	<2,0	Recurr	Recurr	NOS (10)	10	High
Jung et al. (2019)	Prospective Observational	Pre Pre Post Post	50–74 50–74 50–74 50–74	504 720 692 657	≥7,5 <7,5 ≥7,5 4,9–17,3	818 693	No Exercise	Recurr/ DRBC	Corrected	NOS (7,8)	7,8	Moderate-High
Nechuta et al. (2016)	Cohort Study	Post Post	20–83 20–83	2186 2243	≥17,4 0,1–11,9	2167	<4,9	Recurr/ DRBTWR	Corrected	NOS (10)	10	High
Schmidt et al. (2013)	Case-Control Study	Pre Pre Pre Pre	50–74 50–74 50–74 50–74	833 687 619 579	12,0–23,9 24,0–41,9 >41,9 3,0–8,9	675	No Exercise	Recurr	Recurr	NOS (6,7)	6,7	Moderate

Abbreviations. Assess Time = Time of assessment (pre or post-therapy); Ne = Number of exposed participants; Nne = Number of non-exposed participants; DFS = Disease Free Survival; Recurr = Recurrence; DRBC = Death Related with Breast Cancer; NPBC = New Primary Breast Cancer; DRBTWR = Death Related with Breast Cancer Without Recurrence; RCT = Randomized Controlled Trial; NOS = Newcastle Ottawa Scale; PEDro = Physiotherapy Evidence Database Scale.

Table 3
Main findings in meta-analyses.

		SUMMARY OF FINDINGS										
		EFFECT SIZE					PUBLICATION BIAS			HETEROGENEITY		
		K	N	N_s	RR	95% CI	Funnel Plot (*p*-value for Egger)	Trim-and-fill (% var)	Risk	I^2 (%)	Q-test (*p*-value)	Risk
BREAST CANCER RECURRENCE	**POSTDIAGNOSIS RECREATIONAL PA**	18	20,686	2955.1	0.84	0.78 to 0.91	Symmetric (*p* 0.37)	0%	No	0.15%	17.03 (*p* 0.45)	No
	PREDIAGNOSIS RECREATIONAL PA	7	6044	2014.7	0.82	0.74 to 0.91	Slightly asymmetric (*p* 0.02)	0%	No	0.35%	6.02 (*p* 0.43)	No
DISEASE FREE SURVIVAL	**POSTDIAGNOSIS RECREATIONAL PA**	4	2877	1438.5	0.77	0.66 to 0.93	Slightly asymmetric (*p* 0.13)	4%	No	0%	2.99 (*p* 0.39)	No

Abbreviations: K=Number of comparisons; N = Total Sample Size; Ns = Participants per Study; RR = Relative Risk; 95% CI = 95% Confidence Interval; % var = Percentage of variation; PA=Physical Activity.

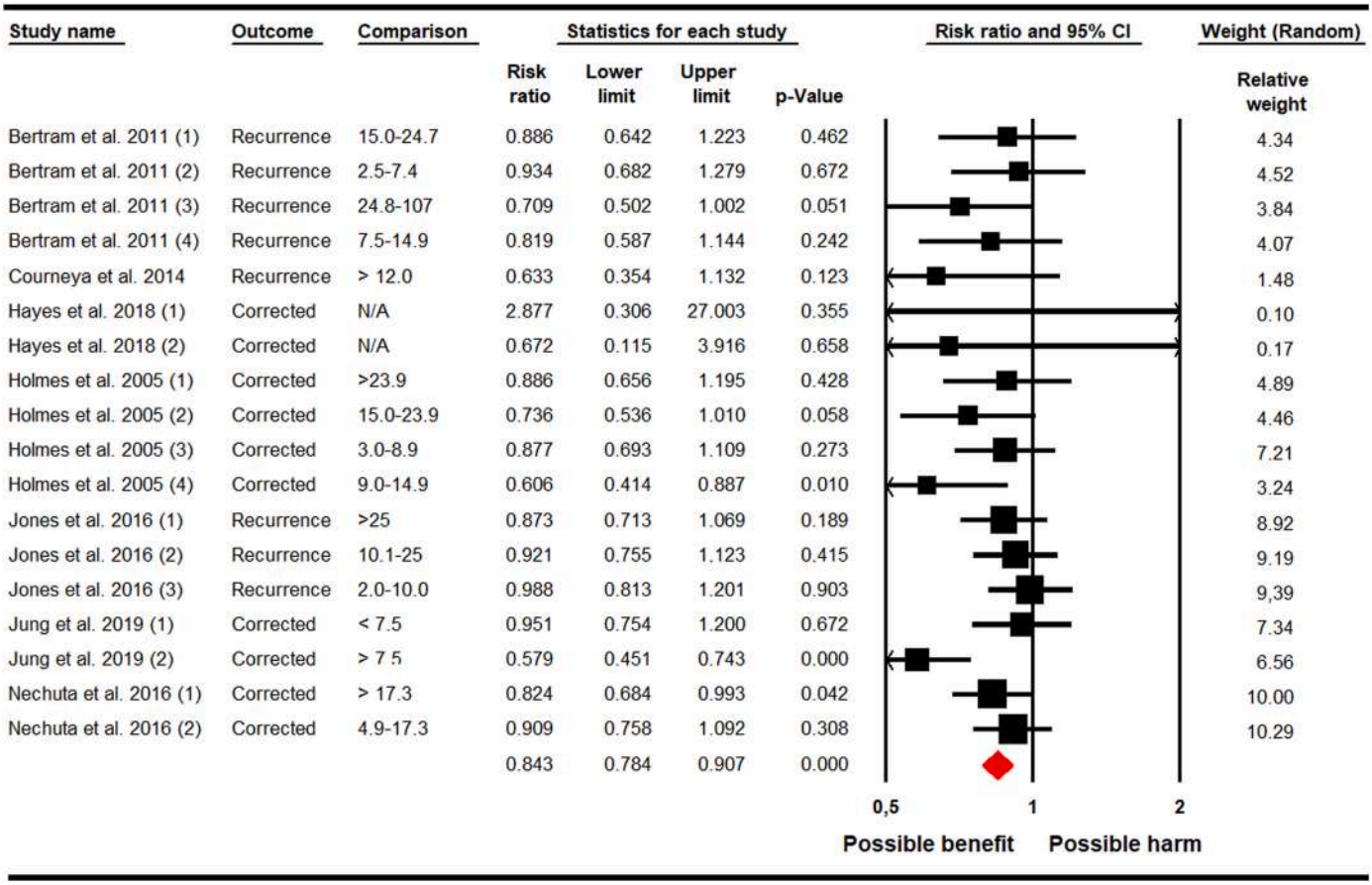

Fig. 2. Forest plot of the postdiagnosis recreational physical activity in breast cancer recurrence.

3.5. Prediagnosis recreational physical activity in breast cancer recurrence

We included 7 independent comparisons from 3 studies (Friedenreich et al., 2009; Jung et al., 2019; Schmidt et al., 2013). We found a negative and significant relationship between prediagnosis PA and recurrence of BC (RR, 0.82; 95% CI: 0.74 to 0.91; n = 6044; average sample size: 2014.7) (Table 3, Fig. 3). Prediagnosis recreational PA reduces the risk of BC recurrence by 18%. The methodological quality of the included studies was moderate to high (8.1 ± 1.4) with a low-quality evidence. There was evidence of very low heterogeneity (Q, 6.021; df: 6; p-value for Q, 0.43; I^2: 0.35%). The funnel plot seemed asymmetrical (p for Egger's test, 0.02) (Supplementary Online Fig. 2) showing a possible risk of publication bias that could slightly overestimate the pooled effect. However, trim and fill estimation did not find variation respect the original pooled effect.

When quantitative meta-regression was carried out, it did not explain any level of heterogeneity according to the quality of the included studies ($p = 0.34$). Leave-one-out analyses yielded a variation of 5% respect the pooled. Analysis including comparison means per study showed little variation in the pooled effect (RR, 0.82; 95% CI: 0.74 to 0.91). We could not carry out subgroup analyses due to the scarce number of independent comparisons included.

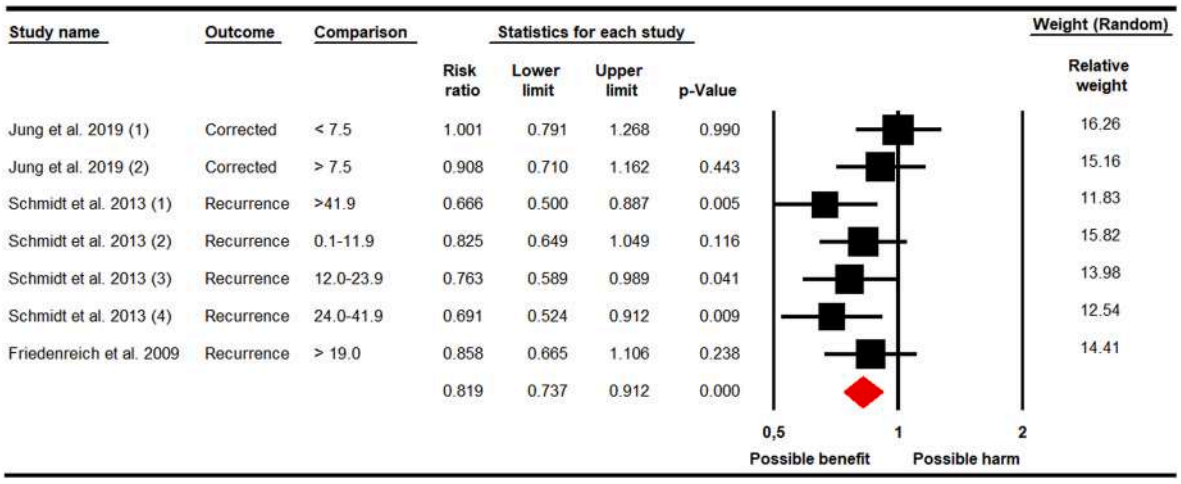

Fig. 3. Forest plot of the pretdiagnosis recreational physical activity in breast cancer recurrence.

3.6. Postdiagnosis recreational physical activity in recurrence/disease-specific mortality

We included 4 independent comparisons from 2 studies (Bao et al., 2015; Chen et al., 2011). We found a negative and significant relationship between postdiagnosis recreational PA and DFS events (RR, 0.77; 95% CI: 0.66 to 0.93; n = 2877; average sample size: 1438.5) (Table 3, Fig. 4). Thus, postdiagnosis PA reduces the recurrence/disease-specific mortality by 23%. The methodological quality of the included studies was moderate to high (8.9 ± 1.1). There was no evidence of heterogeneity (Q, 2.99; degree of freedom [df], 3; p-value for Q, 0.39; I^2, 0.00%). No risk of publication bias was found (p for Egger's test, 0.13 and trim and fill estimation varied 4% (adjusted RR, 0.8; 95% CI 0.69 to 0.95) respect to the original RR) (Supplementary Online Fig. 3). We could not carry out subgroup analyses due to the scarce number of independent comparisons included.

4. Discussion

This study is the first review that assess the effect of pre and postdiagnosis recreational PA on the risk of BC recurrence in BC surviving women with a large number of studies. We identified 11 studies reporting data from 29,677 women diagnosed with BC, who performed recreational PA. This review shows interesting results, so postdiagnosis recreational PA reduces the risk of BC recurrence by 16%, and prediagnosis by 18%. In addition, postdiagnosis recreational PA reduces the risk of DFS events (recurrence/disease specific mortality) by 23%. Our review differentiates of previous published reviews so: (1) includes a large number of studies; (2) analyzes if findings are robust with sensitivity and sub-groups analysis; and (6) finally, includes an assessment of the quality of the studies included in each meta-analysis.

Approximately 20–40% of patients with cancer (including BC) show a high level of physical inactivity. The American College of Sports Medicine (ACSM) recommends the regular practice of different modalities of PA to reduce the negative impact of BC, its recurrence or mortality (Garber et al., 2011). Practicing aerobic PA reduces BC-related fatigue and increases muscle endurance and bone density. A recent systematic review and meta-analysis reported that PA may reduce the risk of cardiovascular disorders due to the maintenance of a sedentary lifestyle that some women with BC carry out after BC diagnosis (Wang et al., 2021). Regarding psychological health, physical exercise reduces BC-related mental overload, anxiety, depression, and coping and improves sleep quality. The improvement of physical and mental components increases the quality of life and the social relationships of women with BC (Schutz et al., 2021). According to ACSM recommendations, women with a high risk of BC have 50% reduced hazards of recurrence and mortality (Cannioto et al., 2021).

A previous meta-analysis of observational studies showed that postdiagnosis recreational PA produces a positive effect on BC mortality and probably on its recurrence (Spei et al., 2019). Our study reinforces the idea that PA after diagnosis during rehabilitation reduces the risk of BC recurrence by 16%. In addition, our meta-analysis shows how performing recreational PA before BC diagnosis could reduce the risk of recurrence by 18%, which makes recreational PA an excellent therapy to be used in the prevention of BC in middle-aged women. Therefore, it is recommended to include therapies based on leisure and structured recreational PA in the rehabilitation program of women with BC due to the important risk reduction of BC relapse. Some studies have reported

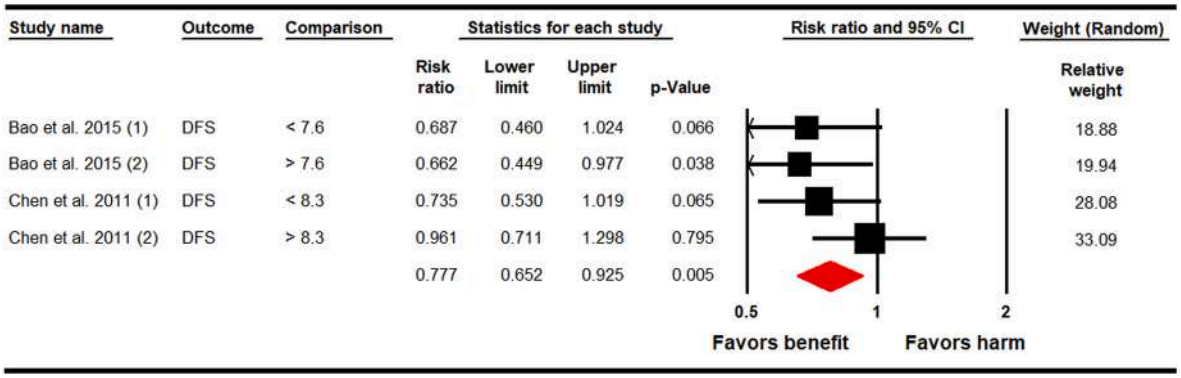

Fig. 4. Forest plot postdiagnosis recreational physical activity in recurrence/disease-specific mortality.

that PA produces a protective effect to reduce the recurrence of BC and has a relevant role in BC cancer prevention (Maeng, 2012). This may be explained by the effect of PA on biological mechanisms, such as sex steroids and metabolic hormones, inflammatory markers, cytokines and adipokines, myokines and stress hormones and other factors, such as plasma metabolites related to PA, oxidative stress of cells and circulating microRNAs (Hong and Lee, 2020). In postmenopausal women, the reduction of oestradiol increases the body mass index, and the level of adiposity is related to a high risk of BC (Liedtke et al., 2011). In addition, higher levels of plasma insulin show a large relation with BC recurrence in survivors (Gunter et al., 2009). The presence of high levels of interleukin 1 and 6, C-reactive proteins and tumour necrosis factor alpha considerably increases the risk of BC and its recurrence (Il'yasova et al., 2005). Different studies have shown that PA reduces the number of circulating sex hormones and reduces weight and body fat mass, regulating inflammatory cytokines and adipokines, and it can be responsible for the reduction in BC recurrence (Hong and Lee, 2020).

In contrast to other therapies in BC, such as chemotherapy or radiotherapy, surviving women with BC reported that recreational PA is a motivating therapy that favours the adherence of rehabilitation programs (Pudkasam et al., 2018). In this sense, recreational PA increases the level of functional capacity in these women due to the reduction of body mass and improves the psychological overload related to isolation and loss of own confidence. Normally, PA training is carried out in groups of women with the same problem, increasing the socialization of these patients and favouring the sharing of cancer experiences that can help these patients to make the path with the disease more bearable (Pudkasam et al., 2018).

This systematic review with meta-analysis present some strengths. Our findings about recurrence are estimated with a large number of participants included in each meta-analysis; the low risk of publication bias and no heterogeneity; the acceptable methodological quality of the studies included; and the robustness of findings.The results of our review show important clinical implications, since support the use of PA as conservative and non-invasive therapy, with few side effects or adverse events, to reduce the recurrence of BC and reduce the recurrence/disease-specific mortality. In addition, recreational PA is presented as a form of playful and group physical exercise, which is practiced at low-moderate intensity and with pauses, which can generate greater adherence and favours that surviving women with BC practice it more frequently. Recreational PA along with a non-sedentary lifestyle and a healthy diet is an excellent preventive tool for BC or its recurrence. Health professionals such as nurses or physiotherapists must be able to implement individualized or group recreational PA programs in women who do not yet have BC or who have successfully overcome it.

Although this review presents interesting findings, some limitations may be considered. First, the inclusion of different research designs including observational and clinical trials reduces the quality evidence. Second, it is important to highlight the low number of studies although they were the only ones available that met all the inclusion criteria. Thirdly, the possible risk of publication bias in meta-analyses with lowest comparisons that can underestimate or overestimate the findings. Finally, it is important to remark that, although recurrence/disease-specific mortality was also analyzed secondarily, the number of studies was small due to, probably, to incomplete searches. In future, it is necessary to increase the number of clinical trials that assess the effect of recreational PA in these outcomes, minimizing risks and increasing the generalization of its findings. Applied to clinical practice, it is essential that health professionals recommend the practice of regular recreational PA or PA to prevent or reduce the risk of BC, among other prevalent and disability pathologies.

5. Conclusion

In conclusion, findings present in this systematic review with meta-analysis shows that prediagnosis and postdiagnosis recreational PA reduces the risk of BC recurrence. In addition, postdiagnosis PA reduces the recurrence/disease-specific mortality in patients with BC. Therefore, our findings reinforce the idea to include recreational PA in the rehabilitation programs of women with BC with the aim to prevent future events or recurrence.

Authors contributions

Conceptualization, NZA, MJMR and RDPC; methodology, RDPC and EOG; software, E.O.-G. and RDPC; validation, NZA and MJMR; formal analysis, NZA, MJMR, EOG and RDPC; data curation, MJMR, NZA and RDPC.; writing—original draft preparation, NZA and EOG; writing—review and editing, MJMR and RDPC; visualization, NZA, MJMR, EOG and RDPC; supervision, RDPC; project administration, RDPC. All authors have read and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejon.2022.102162.

References

Ahmad, A., 2019. Breast cancer statistics: recent trends. Adv. Exp. Med. Biol. 1152, 1–7. https://doi.org/10.1007/978-3-030-20301-6_1.

Ansa, B., Yoo, W., Whitehead, M., Coughlin, S., Smith, S., 2015. Beliefs and behaviors about breast cancer recurrence risk reduction among African American breast cancer survivors. Int. J. Environ. Res. Publ. Health 13. https://doi.org/10.3390/ijerph13010046.

Bao, P.-P., Zhao, G.-M., Shu, X.-O., Peng, P., Cai, H., Lu, W., Zheng, Y., 2015. Modifiable lifestyle factors and triple-negative breast cancer survival: a population-based prospective study. Epidemiology 26, 909–916. https://doi.org/10.1097/EDE.0000000000000373.

Bertram, L.A.C., Stefanick, M.L., Saquib, N., Natarajan, L., Patterson, R.E., Bardwell, W., Flatt, S.W., Newman, V.A., Rock, C.L., Thomson, C.A., Pierce, J.P., 2011. Physical activity, additional breast cancer events, and mortality among early-stage breast cancer survivors: findings from the WHEL Study. Cancer Causes Control 22, 427–435. https://doi.org/10.1007/s10552-010-9714-3.

Borenstein, M., Hedges, L., Higgins, J., Rothstein, H., 2020. Comprehensive Meta-Analysis Software Version 3.

Cannioto, R.A., Hutson, A., Dighe, S., McCann, W., McCann, S.E., Zirpoli, G.R., Barlow, W., Kelly, K.M., DeNysschen, C.A., Hershman, D.L., Unger, J.M., Moore, H. C.F., Stewart, J.A., Isaacs, C., Hobday, T.J., Salim, M., Hortobagyi, G.N., Gralow, J. R., Albain, K.S., Budd, G.T., Ambrosone, C.B., 2021. Physical activity before, during, and after chemotherapy for high-risk breast cancer: relationships with survival. J. Natl. Cancer Inst. 113, 54–63. https://doi.org/10.1093/jnci/djaa046.

Chen, X., Lu, W., Zheng, W., Gu, K., Matthews, C.E., Chen, Z., Zheng, Y., Shu, X.O., 2011. Exercise after diagnosis of breast cancer in association with survival. Cancer Prev. Res. 4, 1409–1418. https://doi.org/10.1158/1940-6207.CAPR-10-0355.

Chong, F., Wang, Y., Song, M., Sun, Q., Xie, W., Song, C., 2021. Sedentary behavior and risk of breast cancer: a dose–response meta-analysis from prospective studies. Breast Cancer 28, 48–59. https://doi.org/10.1007/s12282-020-01126-8.

Cooper, H., Hedges, L.V., Valentine, J.C., 2009. The Handbook of Research Synthesis and Meta-Analysis. Russell Sage Foundation.

Courneya, K.S., Segal, R.J., McKenzie, D.C., Dong, H., Gelmon, K., Friedenreich, C.M., Yasui, Y., Reid, R.D., Crawford, J.J., Mackey, J.R., 2014. Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. Med. Sci. Sports Exerc. 46, 1744–1751. https://doi.org/10.1249/MSS.0000000000000297.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7, 177–188. https://doi.org/10.1016/0197-2456(86)90046-2.

Duval, S., Tweedie, R., 2000. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56, 455–463. https://doi.org/10.1111/j.0006-341X.2000.00455.x.

Egger, M., Smith, G.D., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple , graphical test measures of funnel plot asymmetry. Br. Med. J. 315, 629–634. https://doi.org/10.1136/bmj.315.7109.629.

Engelhardt, E.G., Garvelink, M.M., De Haes, J.C.J.M., Van Der Hoeven, J.J.M., Smets, E. M.A., Pieterse, A.H., Stiggelbout, A.M., 2014. Predicting and communicating the risk of recurrence and death in women with early-stage breast cancer: a systematic review of risk prediction models. J. Clin. Oncol. 32, 238–250. https://doi.org/10.1200/JCO.2013.50.3417.

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D., Bray, F., 2015. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer 136, E359–E386. https://doi.org/10.1002/ijc.29210.

Friedenreich, C.M., Gregory, J., Kopciuk, K.A., Mackey, J.R., Courneya, K.S., 2009. Prospective cohort study of lifetime physical activity and breast cancer survival. Int. J. Cancer 124, 1954–1962. https://doi.org/10.1002/ijc.24155.

Friedenreich, C.M., Neilson, H.K., Farris, M.S., Courneya, K.S., 2016. Physical activity and cancer outcomes: a precision medicine approach. Clin. Cancer Res. 22, 4766–4775. https://doi.org/10.1158/1078-0432.CCR-16-0067.

Garber, C.E., Blissmer, B., Deschenes, M.R., Franklin, B.A., Lamonte, M.J., Lee, I.M., Nieman, D.C., Swain, D.P., 2011. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med. Sci. Sports Exerc. 43, 1334–1359. https://doi.org/10.1249/MSS.0b013e318213fefb.

Gunter, M.J., Hoover, D.R., Yu, H., Wassertheil-Smoller, S., Rohan, T.E., Manson, J.E., Li, J., Ho, G.Y.F., Xue, X., Anderson, G.L., Kaplan, R.C., Harris, T.G., Howard, B.V., Wylie-Rosett, J., Burk, R.D., Strickler, H.D., 2009. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J. Natl. Cancer Inst. 101, 48–60. https://doi.org/10.1093/jnci/djn415.

Hayes, S.C., Steele, M.L., Spence, R.R., Gordon, L., Battistutta, D., Bashford, J., Pyke, C., Saunders, C., Eakin, E., 2018. Exercise following breast cancer: exploratory survival analyses of two randomised, controlled trials. Breast Cancer Res. Treat. 167, 505–514. https://doi.org/10.1007/s10549-017-4541-9.

Higgins, J., Thomas, J., 2020. Cochrane Handbook for Systematic Reviews of Interventions, second ed. Wiley Blackwell & Sons, Hoboken, NJ. Wiley, 2nd ed. ed.

Higgins, J., Thompson, S., Deeks, J., Altman, D., 2003. Measuring inconsistency in meta-analyses. Br. Med. J. 327, 557–560. https://doi.org/10.1136/bmj.327.7414.557.

Holmes, M.D., Chen, W.Y., Feskanich, D., Kroenke, C.H., Colditz, G.A., 2005. Physical activity and survival after breast cancer diagnosis. JAMA 293, 2479–2486. https://doi.org/10.1001/jama.293.20.2479.

Holtermann, A., Krause, N., van der Beek, A.J., Straker, L., 2018. The physical activity paradox: six reasons why occupational physical activity (OPA) does not confer the cardiovascular health benefits that leisure time physical activity does. Br. J. Sports Med. 52, 149–150. https://doi.org/10.1136/bjsports-2017-097965.

Hong, B.S., Lee, K.P., 2020. A systematic review of the biological mechanisms linking physical activity and breast cancer. Phys. Act. Nutr. 24, 25–31. https://doi.org/10.20463/pan.2020.0018.

Il'yasova, D., Colbert, L.H., Harris, T.B., Newman, A.B., Bauer, D.C., Satterfield, S., Kritchevsky, S.B., 2005. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. Cancer Epidemiol. Biomarkers Prev. 14, 2413–2418. https://doi.org/10.1158/1055-9965.EPI-05-0316.

Jones, L.W., Kwan, M.L., Weltzien, E., Chandarlapaty, S., Sternfeld, B., Sweeney, C., Bernard, P.S., Castillo, A., Habel, L.A., Kroenke, C.H., Langholz, B.M., Queensberry, C.P.J., Dang, C., Weigelt, B., Kushi, L.H., Caan, B.J., 2016. Exercise and prognosis on the basis of clinicopathologic and molecular features in early-stage breast cancer: the LACE and pathways studies. Cancer Res. 76, 5415–5422. https://doi.org/10.1158/0008-5472.CAN-15-3307.

Jung, A.Y., Behrens, S., Schmidt, M., Thoene, K., Obi, N., Hüsing, A., Benner, A., Steindorf, K., Chang-Claude, J., 2019. Pre- to postdiagnosis leisure-time physical activity and prognosis in postmenopausal breast cancer survivors. Breast Cancer Res. 21, 117. https://doi.org/10.1186/s13058-019-1206-0.

Lahart, I.M., Metsios, G.S., Nevill, A.M., Carmichael, A.R., 2015. Physical activity, risk of death and recurrence in breast cancer survivors: a systematic review and meta-analysis of epidemiological studies. Acta Oncol. (Madr.) 54, 635–654. https://doi.org/10.3109/0284186X.2014.998275.

Lee, Jongin, Lee, JaeYong, Lee, D., Kim, H., Kang, M., 2021. Sedentary work and breast cancer risk: a systematic review and meta-analysis. J. Occup. Health 63. https://doi.org/10.1002/1348-9585.12239.

Liedtke, S., Schmidt, M.E., Becker, S., Kaaks, R., Zaineddin, A.K., Buck, K., Flesch-Janys, D., Wahrendorf, J., Chang-Claude, J., Steindorf, K., 2011. Physical activity and endogenous sex hormones in postmenopausal women: to what extent are observed associations confounded or modified by BMI? Cancer Causes Control 22, 81–89. https://doi.org/10.1007/s10552-010-9677-4.

Macedo, L.G., Elkins, M.R., Maher, C.G., Moseley, A.M., Herbert, R.D., Sherrington, C., 2010. There was evidence of convergent and construct validity of Physiotherapy Evidence Database quality scale for physiotherapy trials. J. Clin. Epidemiol. 63, 920–925. https://doi.org/10.1016/j.jclinepi.2009.10.005.

Maeng, J.-S., 2012. Food, nutrition, physical activity and cancer: a global perspective and analysis of the research. Bull. Food Technol. 25, 2–26.

Marzo-Castillejo, M., Vela-Vallespín, C., Bellas-Beceiro, B., Bartolomé-Moreno, C., Ginés-Díaz, Y., Melús-Palazón, E., 2020. Grupos de Expertos de Cáncer del PAPPS. Recomendaciones de Prevención del Cáncer. Actualización PAPPS 2020. Atención Primaria 52, 44–69. https://doi.org/10.1016/j.aprim.2020.09.003.

Meader, N., King, K., Llewellyn, A., Norman, G., Brown, J., Rodgers, M., Moe-Byrne, T., Higgins, J.P., Sowden, A., Stewart, G., 2014. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. Syst. Rev. 3, 82. https://doi.org/10.1186/2046-4053-3-82.

Nechuta, S., Chen, W.Y., Cai, H., Poole, E.M., Kwan, M.L., Flatt, S.W., Patterson, R.E., Pierce, J.P., Caan, B.J., Ou Shu, X., 2016. A pooled analysis of post-diagnosis lifestyle factors in association with late estrogen-receptor-positive breast cancer prognosis. Int. J. Cancer 138, 2088–2097. https://doi.org/10.1002/ijc.29940.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Br. Med. J. 372, n71. https://doi.org/10.1136/bmj.n71.

Pazmino, L., Esparza, W., Aladro-Gonzalvo, A.R., León, E., 2021. Impact of work and recreational physical activity on prediabetes condition among U.S. Adults: NHANES 2015–2016. Int. J. Environ. Res. Publ. Health 18, 1378. https://doi.org/10.3390/ijerph18041378.

Peterson, R.A., Brown, S.P., 2005. On the use of beta coefficients in meta-analysis. J. Appl. Psychol. 90, 175–181. https://doi.org/10.1037/0021-9010.90.1.175.

Piercy, K.L., Troiano, R.P., Ballard, R.M., Carlson, S.A., Fulton, J.E., Galuska, D.A., George, S.M., Olson, R.D., 2018. The physical activity Guidelines for Americans. JAMA 320, 2020–2028. https://doi.org/10.1001/jama.2018.14854.

Pudkasam, S., Polman, R., Pitcher, M., Fisher, M., Chinlumprasert, N., Stojanovska, L., Apostolopoulos, V., 2018. Physical activity and breast cancer survivors: importance of adherence, motivational interviewing and psychological health. Maturitas 116, 66–72. https://doi.org/10.1016/j.maturitas.2018.07.010.

Rothman, K., Greenland, S., Lash, T., 2008. Modern Epidemiology. Lippincott Williams & Wilkins, Philadelphia.

Saadatmand, S., Bretveld, R., Siesling, S., Tilanus-Linthorst, M.M.A., 2015. Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173 797 patients. Br. Med. J. 351 https://doi.org/10.1136/bmj.h4901.

Sancho-Garnier, H., Colonna, M., 2019. Breast Cancer Epidemiology. Press, Medicale. https://doi.org/10.1016/j.lpm.2019.09.022.

Schmidt, M.E., Chang-Claude, J., Vrieling, A., Seibold, P., Heinz, J., Obi, N., Flesch-Janys, D., Steindorf, K., 2013. Association of pre-diagnosis physical activity with recurrence and mortality among women with breast cancer. Int. J. Cancer 133, 1431–1440. https://doi.org/10.1002/ijc.28130.

Schünemann, H., Brożek, J., Guyatt, G., Oxman, A., 2017. Manual GRADE (Grading of Recommendations, Assessment, Development and Evaluation). Bogotá: Javierana GRADE Center. Javierana GRADE Center, Bogotá, 2017.

Schutz, S., Aidar, F.J., Souza, R.L.M., dos Santos, J.L., Voltarelli, F.A., Vieira Junior, R.C., Soares, N.M.M., Marçal, A.C., 2021. Different methods of physical training applied to women breast cancer survivors: a systematic review. Front. Physiol. 12, 639406 https://doi.org/10.3389/fphys.2021.639406.

Spei, M.E., Samoli, E., Bravi, F., La Vecchia, C., Bamia, C., Benetou, V., 2019. Physical activity in breast cancer survivors: a systematic review and meta-analysis on overall and breast cancer survival. Breast 44, 144–152. https://doi.org/10.1016/j.breast.2019.02.001.

Strasser-Weippl, K., Goss, P.E., 2013. Competing risks in low-risk breast cancer. Am. Soc. Clin. Oncol. Educ. Book 32–39. https://doi.org/10.14694/edbook_am.2013.33.32.

Wang, S., Yang, T., Qiang, W., Shen, A., Zhao, Z., Chen, X., Xi, C., Liu, H., Guo, F., 2021. Effectiveness of physical exercise on the cardiovascular system in breast cancer patients: a systematic review and meta-analysis of randomized controlled trials. Compl. Ther. Clin. Pract. 44, 101426 https://doi.org/10.1016/j.ctcp.2021.101426.

Wells, G., Shea, B., O'Connel, D., 2009. The Newcastle-Ottawa Scale (NOS) for Assessing the Quailty of Nonrandomised Studies in Meta-Analysis. University of Ottawa. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.