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Original article

Physical activity in breast cancer survivors: A systematic review and meta-analysis on overall and breast cancer survival

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ABSTRACT

Aim: To further quantify the association between physical activity (PA) after breast cancer diagnosis and all-cause mortality, breast cancer mortality and/or breast cancer recurrence.

Methods and results: PubMed was searched until November 2017 for observational studies investigating any type of PA in association with total mortality, breast cancer mortality and/or breast cancer recurrence among women with breast cancer diagnosis. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using random-effects models for highest versus lowest categories of PA. Ten studies were included in the meta-analysis. During an average follow-up ranging from 3.5 to 12.7 years there were 23,041 breast cancer survivors, 2,522 deaths from all causes, 841 deaths from breast cancer and 1,398 recurrences/remissions. Compared to women in the lowest recreational PA level (lowest quintile/quartile), women in the highest level had a lower risk of all-cause mortality (HR = 0.58, 95% CIs: 0.45–0.75; 8 studies), of death from breast cancer (HR = 0.60, 95% CIs 0.36–0.99; 5 studies) and a lower, albeit non-significant, risk of recurrence (HR = 0.79, 95% CIs 0.60–1.05; 5 studies). There was evidence of heterogeneity between the studies evaluating recreational PA and total mortality ($I^2 = 52.4\%$) and even higher for breast cancer mortality ($I^2 = 77.7\%$) or recurrence ($I^2 = 66.4\%$).

Conclusion: Highest recreational PA after breast cancer diagnosis was associated with lower all-cause and breast cancer mortality. This finding probably reflects the favorable impact of PA on cardiovascular mortality, and a possible favorable role on breast cancer survival, though reverse causation cannot be excluded.

1. Introduction

Established risk factors for breast cancer are low or late parity, family history of breast cancer, early menarche and late menopause, hormone replacement therapy (HRT) and post-menopausal obesity, while among the probable risk factors is low physical activity [1–3].

There is some evidence that physical activity may also play a role on breast cancer survival. According to the Continuous Update Project Expert Report 2018 of the World Cancer Research Fund (WCRF) the evidence that being physically active decreases the risk of dying earlier among breast cancer survivors is still limited and insufficient to justify specific recommendations [3]. Furthermore, studying the importance of lifestyle factors, such as physical activity among breast cancer survivors is considered complex due to methodological issues such as time frames of assessment, differences in treatments and consideration of reverse causation. Thus currently, recommendations concerning physical activity for cancer survivors are based on extrapolation from the cancer prevention recommendations.

Findings from the most recent meta-analysis, published in 2015, investigating the association between physical activity and risk of death or breast cancer recurrence in breast cancer survivors showed an inverse relationship with all-cause mortality, breast cancer mortality and breast cancer-related events (defined as breast cancer progression, new primaries and recurrence

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Abbreviations

CIs	Confidence Intervals
CUP	Continuous Update Project
ER	Estrogen receptor Status
HR	Hazard Ratio
MET-h/wk	Metabolic Equivalents hours per week
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NOS	Newcastle-Ottawa Scale
HRT	hormone replacement therapy
BMI	Body Mass Index

combined), although substantial heterogeneity among studies was also reported [4]. The magnitude of this association and if possible, the mechanisms through which physical activity (total or specific types) may exert its effects on mortality and recurrence among breast cancer survivors are also of interest [5–16].

Based on the above, we conducted an updated systematic review and meta-analysis of observational studies focusing on physical activity implemented after the diagnosis of breast cancer (post-diagnosis physical activity) including about 1500 additional breast cancer cases and about 200 additional events.

2. Methods

2.1. Search strategy

The systematic review and meta-analysis was conducted following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for reporting [17–19]. The literature search was performed using the electronic database PubMed up to November 2017, with the following key words: ("physical activity" OR exercise OR walking OR sport OR "physical exertion" OR "physical intensity" OR "recreational activity" OR "household activity" OR "occupational activity" OR "metabolic equivalent" OR "vigorous physical activity") AND ("breast cancer" OR "breast cancer survival" OR "breast cancer recurrence" OR "breast cancer survivors") AND (survival OR recurrence OR mortality OR relapse). The search did not include editorials, letters, comments, conference letters, systematic reviews and meta-analyses and it was limited to English articles. References lists of previous meta-analyses and systematic reviews, as well as, from the identified articles in the present review, were also hand-searched in order to retrieve any additional relevant articles.

2.2. Study selection

Studies were eligible to be included if: (i) they had a prospective or case-control design, (ii) examined the association of physical activity with at least one of the primary endpoints of interest, that is, all-cause mortality, breast cancer mortality and/or cancer recurrence, (iii) the study population consisted of women aged 19 + years with a diagnosis of breast cancer (from the time of diagnosis, through and after treatment), (iv) the minimum sample size was 100 participants, (v) the length of follow-up was at least six months, and (vi) provided a measure of association such as Hazard Ratios (HRs) and the corresponding 95% confidence intervals (CIs) for the comparison between the highest versus the lowest categories of physical activity or sufficient information for their calculation. Abstracts and full-texts were independently screened by two authors (ME-S, VB) and disagreement was resolved by consensus with another author (ES).

Following the literature search, studies were screened and the non-relevant ones were excluded: cross-sectional studies, studies using as endpoints quality of life, breast cancer risk, weight loss, behavioural changes, nutrition and survival, racial differences, changes on physical activity, and assessment of recreational physical activity before breast cancer.

2.3. Data extraction

All data were extracted in a standard pre-determined format including information on: first author's name, publication year, study location, study design, cancer type and stage, number of study participants, age, gender, follow-up duration, outcome, particular types, assessment and categories of physical activity (i.e. values from tertiles/quartiles/quintiles used to define the highest category and the lowest category taken as reference), adjustment factors, and the reported measure hazard ratio (HR) with the 95% confidence intervals (CIs) for the association of physical activity with the outcomes of interest. Physical activity was measured in metabolic equivalents in hours per week (MET- h/wk) and we took into account the estimates regarding the highest vs the lowest level of the categories of physical activity that was used in each study (tertile/quartile/quintile). We extracted from each study HR estimates adjusted for the largest number of confounding factors as possible. We also took into account HR estimates stratified by estrogen receptor (ER) status, body mass index (BMI) and time of physical activity assessment from study diagnosis, when provided.

2.4. Quality assessment of included studies

Study quality was assessed using the Newcastle-Ottawa Scale (NOS) a risk of bias assessment tool for observational studies [20]. The NOS assigns up to a maximum of nine points for the studies with the least risk of bias in three domains: 1) selection of participants and study design (four points); 2) comparability of groups (two points); and 3) ascertainment of exposure and outcomes (three points). Scores for low (0–3), moderate (4–6) and high quality studies (7–9) were assigned and a star was awarded for high quality in each domain. In particular, five studies showed moderate scores and the other half high quality scores.

2.5. Statistical analysis

The pooled estimate for the association of physical activity with each of the outcomes of interest was evaluated by combining the study-specific HRs with fixed effects models, or random effects in the presence of heterogeneity. The random variance component was estimated using the approach by Der Simonian and Laird. To explore heterogeneity between the studies the I^2 statistics were used. When I^2 was >0.50% the statistical heterogeneity was considered substantial [21]. Publication bias was assessed by the application of funnel plots and the Egger's and Begg's tests to investigate the asymmetry among the study estimates. Based on the available data from the eligible studies, we considered four different categorizations of physical activity based on its type and intensity: a) recreational physical activity, which refers to physical activity during leisure time and includes various activities such as walking, running, exercise or sports without specifying their intensity, b) moderate to vigorous physical activity and c) moderate intensity physical activity, that both refer to the degree of intensity that is given in various activities, and d) total physical activity which includes all types of physical activity combined such as occupational, household, transportation and recreational activities. Physical activity had to be assessed after breast cancer diagnosis (defined thereafter as post-diagnosis physical activity). Furthermore, we performed sensitivity analysis by omitting one study at a time and assessing its effect on the overall summary HRs as estimated before and after the exclusion of each study. A cumulative meta-analysis over year of publication was also performed. In addition, in order to identify potential sources of heterogeneity, we stratified the meta-analysis by subgroups: by ER status (ER+/-), BMI and time of post diagnosis physical activity. Effect estimates between groups were compared using the Student's t-test. All the analyses were performed using the STATA statistical package (version 13.1; StataCorp, College Station, TX, USA) [22–25].

3. Results

3.1. Study characteristics

The flow diagram of the study selection procedure is provided in Fig. 1. The initial search yielded 3,362 studies. After exclusion of non-relevant studies, 38 studies remained; 5 additional studies were identified through hand search. Further exclusion of meta-analyses and reviews left 10 studies eligible for the meta-analysis.

In Table 1 the main characteristics of the 10 studies included in this meta-analysis are presented. Supplementary Table 2 gives the HRs for subsequent levels of physical activity in the studies considered, and the corresponding numbers of events. Seven studies were conducted in the United States, one in China, one in Denmark and one was multi-center including data from nine European countries. All studies (90%; 9/10) derived from the general population of women except from one which included nurses only [32].

All studies examined post-diagnosis physical activity, eight studies examined recreational physical activity, 2 examined moderate to vigorous physical activity, 2 moderate intensity recreational physical activity, and 2 considered total physical activity, including occupational, transportation, recreational and household activities. The average follow-up ranged from 3.5 years to 12.7 years with minimum of 2 years. The total number of participants was 23,041, including 2,522 total deaths, 841 deaths due to breast cancer and 1,398 recurrences. Each of the ten studies assessed physical activity after breast cancer diagnosis as follows: at the time of enrolment into the study [27,28,31,35], 1–6 months after diagnosis [29], 6 months after diagnosis [26,29,30,32], at the 3-year post diagnosis interview and at baseline [34], year 3 and year 6 [33].

3.2. Post-diagnosis physical activity and breast cancer prognosis

Fig. 2 presents the results of the meta-analysis for each type of post-diagnosis physical activity with total mortality among breast cancer survivors. Compared to women who reported low recreational physical activity (lowest quintile/quartile), women with high levels (highest quintile/quartile) had 42% lower risk of all-cause mortality (random effects HR = 0.58, 95% CIs: 0.45–0.75). There was no evidence of asymmetry in the funnel plots but of significant heterogeneity ($I^2 = 52.4\%$, p-value < 0.10). The summary mortality ratios for the highest versus the lowest levels of moderate to vigorous physical activity and highest versus lowest levels of moderate intensity physical activity were both indicative of inverse associations but were based on two studies each (HR = 0.50, 95% CIs 0.36–0.68, HR = 0.52, 95% CIs 0.39–0.69, respectively). With respect to total physical activity, results were similar but of borderline statistical significance (random effects HR = 0.53, 95% CIs 0.24–1.20) and also based on two studies.

Pooled breast cancer mortality HR comparing the highest to lowest level of recreational physical activity was 0.60 (95% CIs 0.36–0.99). The corresponding value was 0.55 (95% CIs 0.36–0.84) for moderate intensity recreational physical activity (Fig. 3). There was no evidence of asymmetry but significant heterogeneity ($I^2 = 77.7\%$, p-value < 0.10) was observed.

With respect to breast cancer relapse/recurrence, all study-specific HRs were below unity except for the study of Sternfeld et al. (2009) (Fig. 4) [35]. Pooled HRs for recreational and total physical activity were below unity, though not significantly (random effects HR = 0.79, 95% CIs 0.60–1.05, random effects HR = 0.91, 95% CIs 0.61–1.36, respectively) but were based on a smaller number of studies as compared to the meta-analyses of total mortality. There was no evidence of asymmetry but evidence of significant heterogeneity ($I^2 = 66.4\%$, p-value < 0.10) was observed.

3.3. Subgroup analysis

A stratified meta-analysis for the association between physical activity and overall mortality by ER status showed an inverse association among women with positive ER (HR = 0.47, 95% CIs 0.25–0.88, $I^2 = 85.4\%$, p-value < 0.001) whereas the direction of the association was similar, but non-significant, among women with negative ER (random effects HR = 0.50, 95% CIs 0.38–0.66, $I^2 = 13.6\%$, p-value = 0.328). Subgroup analysis regarding women with BMI <25 kg/m^2 and women ≥25 kg/m^2 did not reveal substantial differences (HR for <25 kg/m^2 = 0.44, 95% CIs 0.30–0.64, $I^2 = 51.1\%$, p-value = 0.085, HR for ≥25 kg/m^2 = 0.54, 95% CIs 0.38–0.76, $I^2 = 42.4\%$, p-value = 0.139) with respect to physical activity in all-cause mortality. Again there was no evidence of funnel plot asymmetry, but significant heterogeneity was noted at the overall effect size (HR = 0.49, 95% CIs 0.38–0.62, $I^2 = 42.4\%$, p-value = 0.075).

Finally, we conducted a subgroup analysis stratified by the time at physical activity assessment after breast cancer diagnosis. The studies were divided into two categories: a) those assessing physical activity less than 12 months after breast cancer diagnosis and b) those assessing it after 12 months. For both strata, an inverse association was evident between physical activity and all-cause mortality, although it was significant only among studies that assessed physical activity within 12 months after breast cancer diagnosis (HR for the category ≤12 months = 0.53, 95% CIs 0.37–0.77, $I^2 = 79.7\%$, p-value < 0.001, HR for the category >12 months = 0.62, 95% CIs 0.55–0.71, $I^2 = 0\%$, p-value = 0.802).

3.4. Sensitivity analysis

We conducted a sensitivity analysis focusing only on the impact of recreational physical activity with overall mortality and breast cancer mortality that produced consistent results. In particular, this analysis did not modify the pooled HR, and the cumulative meta-analysis did not show a relevant change between the estimates of HR by publication year in overall mortality and breast cancer mortality (data not shown). We also added the study of Beasley et al. (2012) [36] as a pooling project, excluding the four cohorts that were already included individually in our analysis in order to observe possible differences on the summary effect size. The risk for all-cause mortality decreased among women with high adherence in recreational physical activity levels compared to those with low levels (HR for fixed effects = 0.53, 95% CI 0.47–0.61, $I^2 = 61.6\%$; HR for random effects = 0.50, 95% CIs 0.38–0.66, $I^2 = 61.6\%$). Similar results were observed among recreational physical activity levels and breast cancer mortality (HR for fixed effects models = 0.63, 95% CIs 0.52–0.76, $I^2 = 73.4\%$; HR for random effects models = 0.52, 95% CIs 0.32–0.86, $I^2 = 73.4\%$).

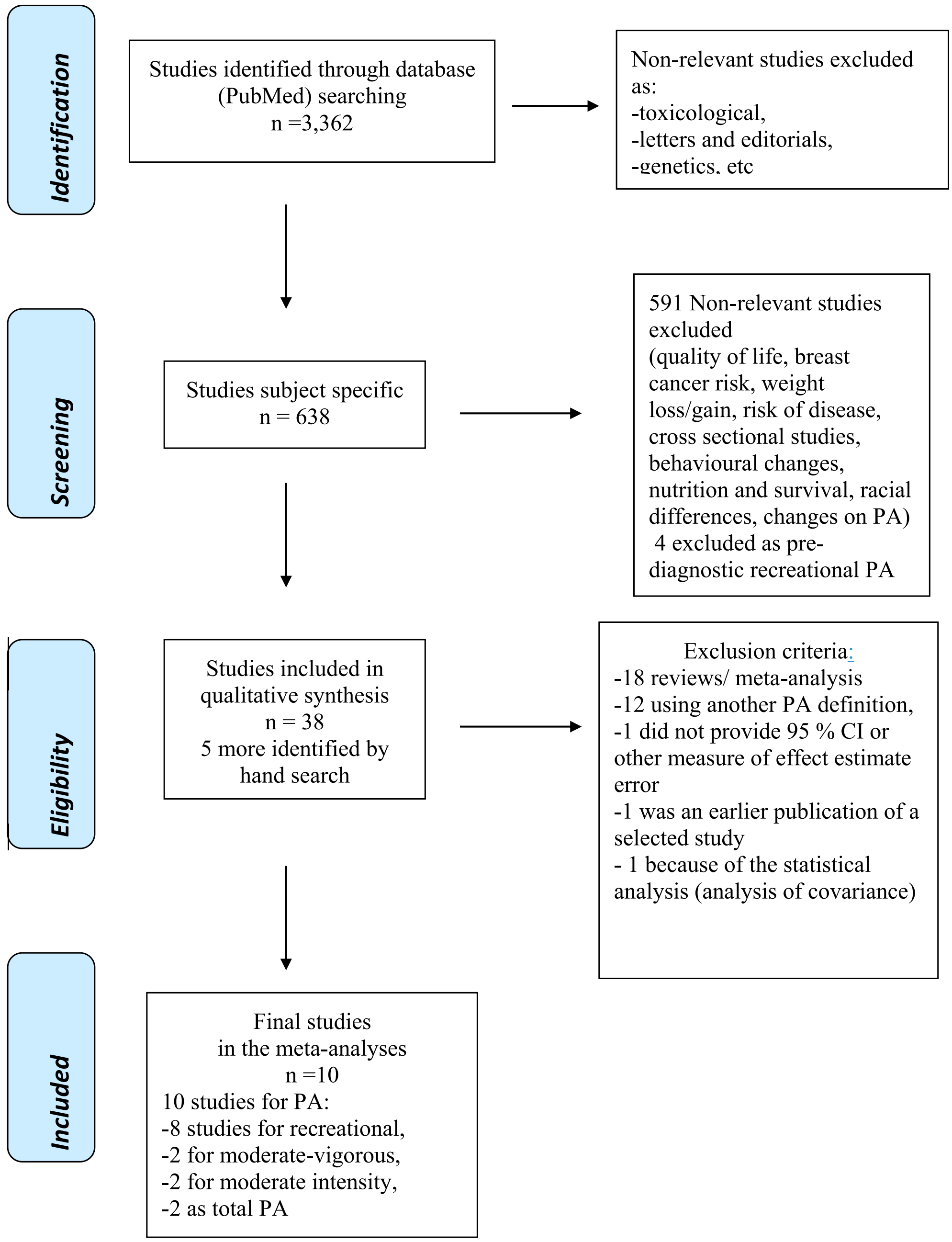

Fig. 1. Flowchart of the study selection process. CI: Confidence Interval, PA: Physical Activity.

4. Discussion

In this updated meta-analysis of observational studies focusing on the role of physical activity undertaken after breast cancer diagnosis women in the highest levels of recreational physical activity had reduced risk of total and breast cancer mortality, by 42% and 40%, respectively in comparison to women in the lowest levels.

Our results are in agreement with the most recent meta-analysis, based on eight prospective cohort studies published until October 2014, which reported a 48% decrease in total mortality and a 41% decrease in breast cancer mortality when comparing the highest levels of post-diagnosis recreational physical activity with the lowest. Our meta-analysis re-evaluates this important research question three years after and investigates only physical activity undertaken after breast cancer diagnosis, a time period which probably is more relevant for breast cancer survivors. Two additional prospective studies of high quality were included in this meta-analysis. The Diet, Cancer, and Health cohort study by Ammitzbøll et al. with 959 breast cancer survivors and 144 deaths which found evidence that exercise was associated with longer survival after controlling for a wide range of important confounders including health behavior, comorbidity and cancer treatment [37] and the Tamoxifen Exemestane Adjuvant Multicenter Lifestyle side study by de Glas et al., with 435 breast cancer survivors and 58 deaths indicating that recreational physical activity after breast cancer diagnosis was associated with improvement in overall survival [38].

Our meta-analysis found considerable heterogeneity among the studies. Efforts to explain this heterogeneity by exploring the differences between cancer survivors in relation to tumor ER status,

Table 1
General characteristics of prospective studies included in meta-analysis reporting the association of physical activity (PA) with all-cause mortality, breast cancer (BC) mortality and/or recurrence among female breast cancer survivors.

Author, year, location	Definition of breast cancer cases, stage (where applicable)	Outcome	N subjects, age range, follow-up duration	PA types studied and categories used	PA assessment tools	Adjustment factors	Summary of results
Ammitzbøll et al., 2016, Denmark	Breast cancer	All-cause mortality	959, 50–64 years, mean follow-up between diagnosis and post-diagnosis PA = 3.5 years	a)Household (housework, do-it-yourself, gardening), b)Exercise (sports, walking, cycling) c)Total PA (MET hrs/wk) Five groups (inactive and quartiles among active)	Questionnaire, validated	alcohol, smoking status, BMI, comorbidity, education, nodal status, operation type, chemotherapy.	After diagnosis of BC, exercise PA ($\geq$2.5 h of brisk walking/week) may reduce mortality up to 32% vs to low levels. Being active in exercise PA had 44% lower risk compared to inactive.
Bradshaw et al., 2014, United States	Breast cancer (in situ or invasive BC)	Death from any cause and death from breast cancer	1,423, 25–91 years, Median survival time = 12.7 years	Recreational (in MET hrs/wk), Three categories	Interview-administered questionnaire	age, pre-diagnosis BMI, chemotherapy, treatment, tumor size	Greater levels of recreational PA after BC diagnosis were associated with substantially lower risk of death from any cause and from BC.
De Glas et al., 2014, nine countries	Breast cancer	Overall survival, breast cancer-survival, and relapse-free survival	435, 63,6 years (median age), hormone receptor-positive women, follow-up duration = until August 15, 2012	Recreational (walking, cycling, gardening, and sports) (MET hrs/wk) quartiles	Questionnaire, validated	age, number of comorbidities, T stage, N stage, BMI, chemotherapy	Overall survival was better for patients active before and after diagnosis. BC survival and recurrence not sign. associated with PA
Bertram et al., 2011, United States	Breast cancer, primary operable invasive stage I, II, or III	Additional breast cancer events, all-cause mortality	2,361, age categories (<44, 45–54, 55–65, and >65 years), median follow-up = 7.1years	Recreational (walking and three intensity levels of exercise: mild, moderate, or strenuous (with example activities for each level, Moderate-vigorous (MET hrs/wk), quintiles	Self-administered questionnaire, 9-item PA measure, validated	age, race, fruit & veg intake, BMI, menopausal status, tumor type, tumor grade, tumor stage, anti-estrogen use, clinical site, time from diagnosis to randomization, hot flashes, study group	Post-treatment PA was associated with reduced all-cause mortality, but not with additional breast cancer events.
Chen et al., 2011, China	Breast cancer Stage I-III	Total mortality and cancer recurrence/ metastasis or death related to breast cancer for recurrence/ disease-specific mortality	4,826, 20–75 years, women, Median follow-up = 4.3 years	Recreational (Exersice activities) (MET hours/week), tertiles	Intervieweer-administered questionnaire, validated	birth date, BMI, waist-to-hip ratio, menopausal status, income, quality of life, education, soy protein intake, cruciferous veg. intake, tea consumption, chemotherapy, radiotherapy, tamoxifen use, tumor-node metastasis status, estrogen/ progesterone receptor status	Regular exercise after BC was significantly associated with improved overall and disease-free survival, following a dose-response pattern.
Irwin et al., 2011, United States	Invasive breast cancer	Total mortality and breast cancer specific mortality	2,910, 50–79 years, mean follow-up = 3.3 years	Moderate-vigorous intensity (from walking and recreational activities) and moderate intensity recreational (from walking and recreational activities) (MET hours/week), quartiles	Self-administered questionnaire, validated	age, stage, ER, PR, grade, HER2, ethnicity, WHI study arm, previous hormone therapy use, time from diagnosis to PA assessment, BMI, diabetes, alcohol, smoke, total calories, % calories from fat, servings of fruit and vegetables.	Moderate to vigorous intensity PA for $\geq$9 MET h/wk before or after a breast cancer diagnosis may improve survival, even among women reporting low PA prior to diagnosis.
Sternfeld et al., 2009, United States	Breast cancer stage I, II, or IIIa	All-cause mortality, breast cancer mortality and breast cancer recurrence	1,970, 18–79 years, mean follow-up = 7.2 ± 1.5 years	Recreational (sports, exercise, dance and sedentary recreational activities such as reading or socializing) and Total PA (MET hours/week), quartiles and 2 categories	Self-administered questionnaire validated	age, number of positive nodes, stage, weight at 18 y, type of treatment and type of surgery, education, smoking status.	Higher levels of PA (in MET-hours/week of all activities of at least moderate intensity, or simply as hours per week of only moderate (and not vigorous) activity, were associated with reduced risk of recurrence and breast cancer mortality.
Holick et al., 2008, United States	Breast cancer, invasive	Breast cancer mortality, total mortality	4,482, 20–79 years, Mean follow-up = 5.5 ± 1.1 y	Recreational (walking outdoors; running; swimming; tennis, squash, racquetball; calisthenics, aerobics, rowing machine; other aerobic recreation, number of flights) and moderate intensity recreational (activities that	Intervieweer-administered questionnaire, validated	postdiagnosis BMI, postdiagnosis menopausal status, postdiagnosis hormone therapy use, total energy intake/year before enrollment, education, family history of BC, initial treatment modality	Any moderate-intensity recreational PA, such as brisk walking, after diagnosis had lower risk of death compared to being inactive.

Table 1 (*continued*)

Author, year, location	Definition of breast cancer cases, stage (where applicable)	Outcome	N subjects, age range, follow-up duration	PA types studied and categories used	PA assessment tools	Adjustment factors	Summary of results
				expend <6 MET), MET-hrs/ week), quartiles			
Irwin et al., 2008, United States	Breast cancer, local and regional breast cancer	Total deaths and breast cancer deaths	688, 35–64 years, Median follow-up = 6 years	Total PA (MET hours/week), tertiles	Self-administered questionnaire, validated	age, race, disease stage, initial treatment, tamoxifen use, BMI, and fruit/vegetable servings per day.	Any category of PA higher than the reference category (<3 MET-hours/week) was associated with decreased risk of adverse breast cancer outcomes.
Holmes et al., 2005, United States	Breast cancer, stage I, II, or III	Breast cancer mortality, total mortality, recurrence	2,987, 30–55 years, Median follow-up = 8 years	Leisure time PA (walking or hiking outdoors, jogging (>10 min per mile); running (≤10 min per mile); bicycling; swimming laps; tennis; calisthenics, aerobics, aerobic dance, or rowing machine; or squash or racquetball), (MET hours/week), quintiles	Questionnaire validated	age, interval between diagnosis and PA, smoking status, BMI, menopausal status, HRT use, age at first birth, parity, oral contraceptive use, energy intake, energy-adjusted protein intake, disease stage, chemotherapy & tamoxifen treatment	Any category of activity higher than the reference category of less than 3 MET-hours per week was associated with a decreased risk of an adverse breast cancer outcome.

Hormone replacement therapy: HRT.

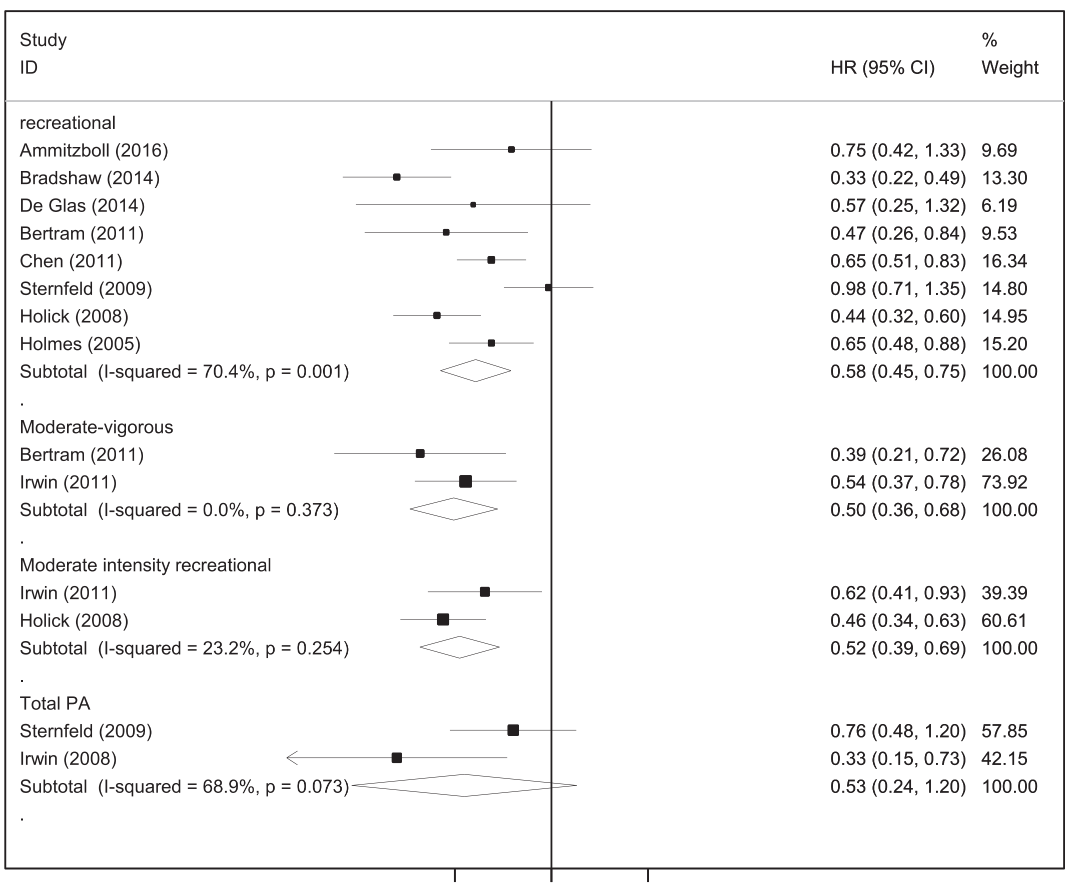

Fig. 2. Forest plot for the association between Physical activity and total mortality in breast cancer survivors. Results from random effects models. CI: Confidence Interval, HR: Hazard Ratio, PA: Physical Activity.

BMI or time of physical activity assessment after cancer diagnosis were not successful. Heterogeneity may be due to methodological differences among the studies, such as the number of confounding factors controlled for in the analysis or the lack of control for important confounders (such as stage of the cancer, treatment) not only after diagnosis but also before diagnosis. It is possible that

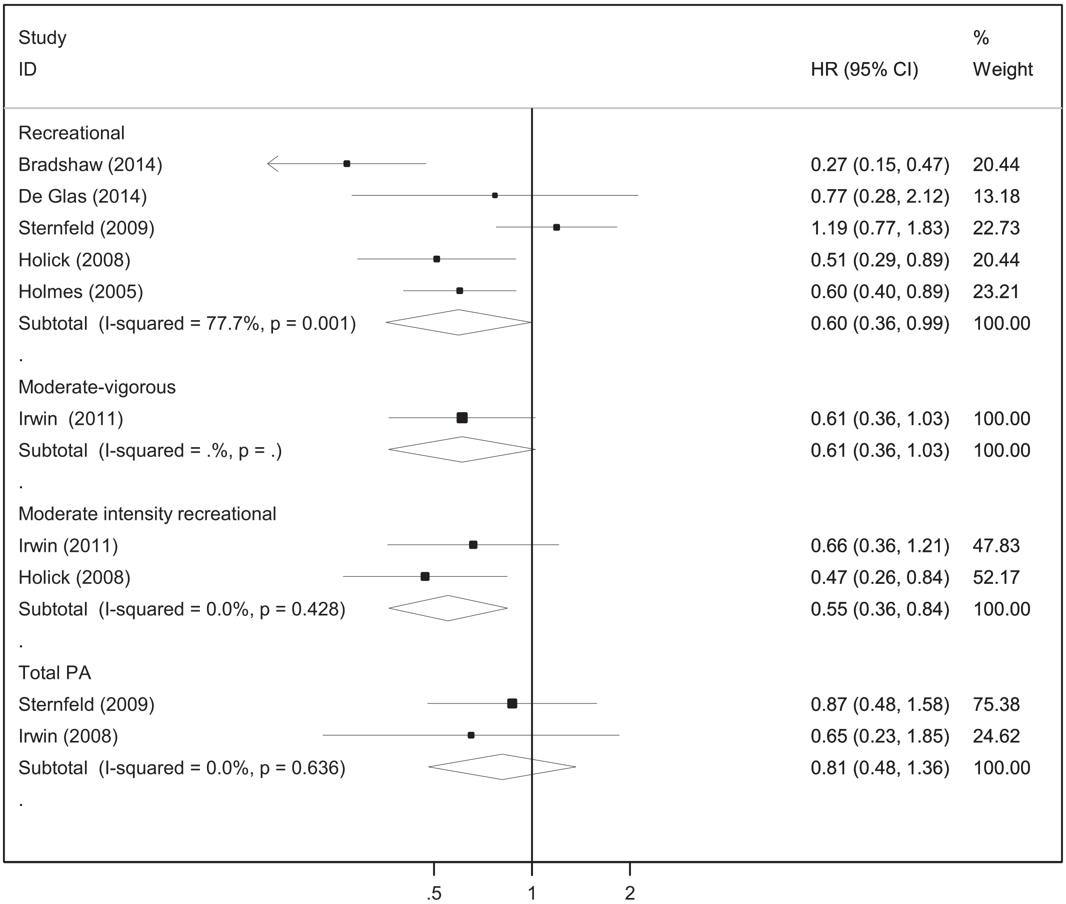

Fig. 3. Forest plot for the association between Physical activity and breast cancer mortality in breast cancer survivors. Results from random effects models. CI: Confidence Interval, HR: Hazard Ratio, PA: Physical Activity.

lifestyle factors, and especially physical activity before diagnosis, have an impact in the association under study.

Also, differences in the definitions of physical activity, in its categorization in levels and in definitions or methods of ascertainment of the primary outcomes (e.g. self-reported or validated information on recurrence), are evident between the studies. Variation in types and duration of treatments between the study participants and number of pre-existing diseases or comorbidities may also create sources of heterogeneity.

Nevertheless, our results are in agreement with many systematic reviews and meta-analyses of observational data [4,8,9,37–44] examining post-diagnostic physical activity among breast cancer survivors that provided evidence for a beneficial effect in reducing risk of total deaths and breast cancer outcomes.

Several biological pathways have been proposed for reducing breast cancer risk, which may also apply for breast cancer survival. These pathways include reduced exposure to estrogen and androgens, insulin and insulin-related factors and adipokines and reduced inflammation. Physical activity may affect these pathways either directly or indirectly by its effect on reducing body weight [4,44,45].

With respect to all-cause mortality the beneficial effect of post-diagnosis recreational physical activity may reflect the favorable impact of regular physical activity on cardiovascular mortality and the development of comorbidities. In fact, physical activity is associated with decreased risk of several chronic diseases, particularly cardiovascular diseases and all cause-mortality [46]. Exercise may be an effective non-pharmacological method of attenuating the harmful effects of breast cancer therapies on the cardiovascular health, by modifying cardiovascular risk factors, and potentially by reducing cardiovascular morbidity and mortality in this vulnerable population. Exercise training may also improve vascular endothelial function and exercise capacity in breast cancer survivors [47]. Other beneficial effects of physical activity in breast cancer patients, although not directly linked to overall survival, cannot be underestimated, such as improvement in physical function, fitness, strength and quality of life, reduction of depression, fatigue and pain, as well as decreased psychological complaints.

Limitations of our analysis include the relatively small number of studies, which also limited the use of meta-regression techniques for the investigation of potential effect modifiers, such as, age and menopausal status. Moreover, the implementation of dose-response meta-analysis was not possible because some of the studies did not provide information about the number of cases in each category of physical activity.

Information on physical activity was self-reported or interview-administered in all studies, thus potentially introducing recall bias. More importantly, reverse causation in the associations reported by the individual studies included in our meta-analysis could explain part of the findings if breast cancer survivors were not engaged in higher levels of recreational physical activity due to symptoms of their disease.

Among the strengths of our study are the inclusion of additional studies in relation to previous meta-analyses with respect to post-diagnosis physical activity [4,13,39], the prospective nature of the included studies and the use of the Newcastle-Ottawa score to

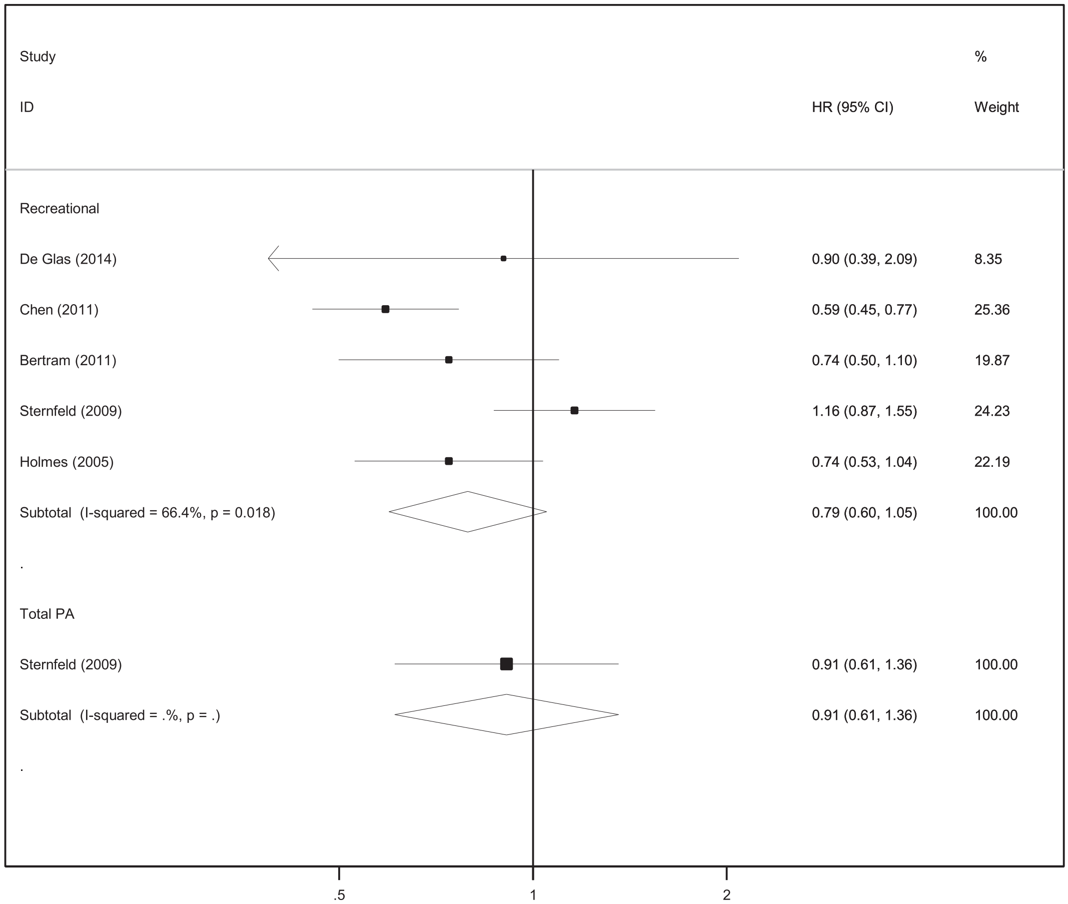

Fig. 4. Forest plot for the association between Physical activity and relapse/recurrence in breast cancer survivors. Results from random effects models. CI: Confidence Interval, HR: Hazard Ratio, PA: Physical Activity.

assess the quality of the studies included in the analysis. We also tried to investigate reasons for between-study heterogeneity conducting subgroup analysis by ER status and BMI or time of physical activity assessment after cancer diagnosis using influence plots and cumulative meta-analysis. Finally, results from Egger's and Begg's tests indicate that publication bias is unlikely.

In conclusion, this meta-analysis supports the beneficial effect of post-diagnostic recreational physical activity on total mortality, breast cancer-specific mortality, and possibly breast cancer recurrence and thus reinforces existing recommendations to be physically active after breast cancer diagnosis. On the other hand, the role of bias, confounding and mainly reverse causation cannot be eliminated in observational studies, particularly with reference to breast cancer specific mortality.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.02.001.

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