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Physical activity and survival after breast cancer diagnosis: meta-analysis of published studies

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Abstract Published data have shown that physical activity (PA) has a positive role on the primary prevention of breast cancer risk. However, the role of PA on breast cancer outcome has been controversial with inconsistent data. The lack of a meta-analysis that addresses that issue prompted the current report. A comprehensive literature search identified eight studies, of which two studies were excluded. The remaining six studies (12,108 patients with breast cancer) were included in this meta-analysis. Pre-diagnosis PA reduced all causes mortality by 18% but had no effect on breast cancer deaths. Post-diagnosis PA reduced breast cancer deaths by 34% (HR = 0.66, 95% CI, 0.57–0.77, $P < 0.00001$), all causes mortality by 41% (HR = 0.59, 95% CI, 0.53–0.65, $P < 0.00001$), and disease recurrence by 24% (HR = 0.76, 95% CI, 0.66–0.87, $P = 0.00001$). Breast cancer mortality was reduced by pre-diagnosis PA in women with body mass index (BMI) < 25 kg/m2, while post-diagnosis PA reduced that risk among those with BMI ≥ 25 kg/m2. On the other hand, post-diagnosis PA reduced all causes mortality regardless of the BMI. The analysis showed that post-diagnosis PA reduced breast cancer deaths (HR = 0.50, 95% CI, 0.34–0.74, $P = 0.0005$), and all causes mortality (HR = 0.36, 95% CI, 0.12–1.03, $P = 0.06$) among patients with estrogen receptor (ER)-positive tumor, while women with ER-negative disease showed no gain. The current meta-analysis provides evidence for an inverse relationship between PA and mortality in patients with breast cancer and supports the notion that appropriate PA should be embraced by breast cancer survivors.

Keywords Breast cancer · Physical activity · Exercise · Prognosis · Mortality

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Introduction

Over the past 20 years, many cohort and case–control studies have examined the role of physical activity in the primary prevention of breast cancer [1–4]. While the evidence has not been always consistent, the findings suggest a significant risk reduction of about 20% to 40% for active compared with sedentary women [4–6]. Moreover, a recent evidence-based review indicated a strong support for 20–80% risk reduction among post-menopausal women and suggested that for each additional hour per week of physical activity, the risk of breast cancer incidence decreased by 6% [7].

However, the role of pre- or post-diagnosis physical activity on breast cancer deaths or on all causes mortality among patients with breast cancer has been controversial. Several studies have suggested a protective role of physical activity on breast cancer outcome [8–12], while others could not demonstrate such benefit [13]. In another study, while physical activity was shown to decrease total mortality, no positive effect was shown on breast cancer recurrence or disease-specific mortality [14].

The inconsistent evidence concerning the role of physical activity on survival of women with invasive breast cancer, the lack of a meta-analysis that addressed that pertinent issue, and the current immense interest in exploring lifestyle factors that could be associated with disease outcome has prompted this meta-analysis. In this report, we systematically reviewed and analyzed all published relevant studies.

Methods

Literature search

We did a comprehensive search of citations from PubMed, proceedings of the main oncology conferences, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Review of Effectiveness. The search was limited to randomized, case–control, cohort, or observational peer-reviewed clinical studies and reviews in English language. Our initial search through each resource used queries with the medical subject headings (MeSH) terms: "breast cancer" OR "breast neoplasm" AND "physical activity" OR "physical activities" OR "exercise", AND "prognosis", AND "recurrence" AND "survival" AND "mortality" in various combinations. The search strategy also used several text terms to identify relevant information. Reference lists from relevant primary studies and review articles were also examined to find other additional publications.

Study selection

We selected for analysis only those randomized, case–control, cohort, or observational peer-reviewed clinical studies where the association between physical activity and breast cancer outcome was investigated.

Statistical methods

Before performing the analyses, data of each published study were carefully checked and verified for coherence with the original publications. Data were entered in a computer database for transfer and statistical analysis in Review Manager Version 5.0.17 (Cochrane Collaboration, Software Update, Oxford, United Kingdom) and Comprehensive Meta Analysis Version 2.2.048 (New Jersey, USA). For trials included in this meta-analysis, if log hazard ratio (HR) and its variance were not presented explicitly, the method reported by Parmar et al., was used to extract estimates of these statistics [15].

In this meta-analysis, both fixed and random effect models were tested where appropriate [16, 17]. X^2 tests were used to study heterogeneity between trials. I^2 statistic was used to estimate the percentage of total variation across studies, due to heterogeneity rather than chance. If the P value was ≤ 0.1, the assumption of homogeneity was deemed invalid, and the random-effects model was reported after exploring the causes of heterogeneity [18]. A two-tailed P value of <0.05 was considered statistically significant. Publication bias was explored through visual inspection of the funnel plots [17]. Findings of the meta-analysis are depicted in classical Forest plots, with point estimates and 95% CIs for each trial and overall; size of the squares is proportional to effect size.

Results

After exclusion of duplicate and irrelevant studies, our search yielded eight eligible published studies that were retrieved for more detailed evaluation [8–14, 19]. For the purpose of this meta-analysis, two studies were excluded. The first study was reported by Borugian et al. [19] and included 603 patients with breast cancer recruited from British Columbia Cancer Agency, Canada. The authors reported several individual adjusted indicators of leisure-time physical activity, but there were no data about total physical activity to permit estimating the overall effect. By and large, there was no observed relationship between any of the activity variables and breast cancer mortality. The second excluded study reported on 1,490 women diagnosed and treated for early stage breast cancer (Women's Healthy Eating and Living study, WHEL) [12]. In the latter study, the effect of physical activity on overall mortality was confounded by the potential influence of the dietary intervention. In the multivariate model, only the combination of consuming ≥ 5 daily servings of vegetables-fruits and accumulating ≥ 9 MET-h/wk was associated with a significant survival advantage (HR = 0.56, 95% CI, 0.31–0.98).

The remaining six studies were included in the meta-analysis. Table 1 depicts the main characteristics of these studies. Four studies included 10,127 patients and mainly assessed the effect of post-diagnosis physical activity on breast cancer outcome [9–11, 14], while two studies (included 1,981 patients) only addressed the potential effect of physical activity in the year prior to diagnosis [8, 13]. In four studies, only the recreational activity was examined [8–10, 13], while two studies estimated all types of physical activity [11, 14].

Table 2 shows the multivariate effect of physical activity on total and breast cancer mortality. Also shown for some studies is the effect of physical activity according to patients' body mass index (BMI) and tumor's receptor status.

As shown in Tables 1 and 2, patients in the included studies were grouped based on the level of their physical activity using different cutoff points. However, with only few exceptions, there were similarities but with some

Table 1 Description of the six studies included in the meta-analysis

Study	Description	No. included	Physical activity	Physical activity after diagnosis, MET-h/wk and (No.) in each group				
Holmes 2005 [10]	Prospective observational study based on questionnaire administered to nurses diagnosed with invasive breast cancer (stage I–III) between 1984 and 1998 in the Nurses' Health Study (NHS) and were followed up until death or June 2002, whichever came first.	2,987	Recreational physical activity at least 2 years after diagnosis measured in Met-h/wk	<3.0 (959)	3–8.9 (862)	9–14.9 (336)	15–23.9 (428)	≥24 (403)
Irwin 2008 [11]	Prospective, a population-based, multicenter observational study based on questionnaire administered to women enrolled onto the Health, Eating, Activity, and Lifestyle Study (HEAL) and who developed invasive breast cancer (stage I–III) between 1995 and 1998 and followed up until death or September 2004, whichever came first.	688	All types of physical activity including recreational, occupational, and household activities measured in MET-h/wk	0 (114)	>0–8.9 (297)	≥9 (277)	–	–
Holick 2008 [9]	Collaborative Women's Longevity Study (CWLS), questionnaire-based to access recent (within the past year) post-diagnosis physical activity and other lifestyle factors in women with the diagnosis of invasive breast cancer (stage I–III) between 1988 and 2001 and were followed up until death or December 2004, whichever came first	4,482	Recreational physical activity within 1 year after diagnosis measured in MET-h/wk	≤2.7 (1,105)	2.8–7.9 (1,072)	8.0–20.9 (1,184)	≥21.0 (1,121)	–
Sternfeld 2009 [14]	Life After Cancer Epidemiology study (LACE), questionnaire-based to access physical activity in women diagnosed with invasive breast cancer (stage I–III) between 1997 and 2000 and were followed up until death or April 2006, whichever came first.	1,970	Moderate–vigorous physical activity (work-related, non-work routine activities, recreational activities, and transportation) measured in MET-h/wk	<5.3 Q1	5.3–<15 Q2	15–<27 Q3	≥27 Q4	–
Abrahamson [8]	Women with invasive breast cancer (localized and regional) diagnosed between 1990 and 1992, were interviewed within several months of diagnosis, and were asked about average moderate and vigorous activity at age 13 years, age 20 years, and during the year prior to diagnosis. Patients were followed up until death or January, 2000 whichever came first.	1,264	Moderate–vigorous recreational physical activity during the year prior to diagnosis measured in relative units and calculated by assigning MET-h/wk for each activity	<16.6 281	16.7–29.4 244	29.5–43.0 271	≥43.1 222	
Enger [13]	Population-based case–control study to assess pre-diagnosis predictors of survival of patients with invasive and non-invasive breast cancer (stage I–III [99%], and stage IV [1%]). Total recreational activity in the year before diagnosis was assessed in face-to-face interviews.	717	Total recreational activity in the year before diagnosis measured as h/w	0 408	1–4 58	≥5 59		

MTE-h/wk, metabolic equivalent task-hours per week; Q, quartile of physical activity

Table 2 Summary of the measured outcomes in the six studies included in the meta-analysis

Study	Outcome	Physical activity (MET-h/wk)					*P* value for trend
		<3.0	3–8.9	9–14.9	15–23.9	≥24	
Holmes 2005 [10]	Breast cancer deaths						
	No. (%)	110 (11.5)	84 (9.7)	20 (6.0)	32 (7.5)	34 (8.4)	
	Multivariable HR (95% CI)	1.00 (Reference)	0.80 (0.60–1.06)	0.50 (0.31–0.82)	0.56 (0.38–0.84)	0.60 (0.40–0.89)	0.004
	Total deaths						
	No. (%)	188 (19.6)	126 (14.6)	38 (11.3)	51 (11.9)	60 (14.9)	
	Multivariable HR (95% CI)	1.00 (Reference)	0.71 (0.56–0.89)	0.59 (0.41–0.84)	0.56 (0.41–0.77)	0.65 (0.48–0.88)	0.003
	Breast cancer recurrence						
	No. (%)	137 (14.3)	108 (12.5)	29 (8.7)	45 (10.5)	51 (12.7)	
	Multivariable HR (95% CI)	1.00 (Reference)	0.83 (0.64–1.08)	0.57 (0.38–0.85)	0.66 (0.38–0.93)	0.74 (0.53–1.04)	0.05
PA prior to diagnosis	BMI < 25 kg/m^2						
	Breast cancer deaths %	13.5	9.2	5.1	8.5	9.8	
	Multivariable HR (95% CI)	1.00 (Reference)	0.65 (0.43–0.97)	0.35 (0.18–0.68)	0.63 (0.39–1.04)	0.61 (0.37–0.99)	0.10
PA prior to diagnosis	BMI > 25 kg/m^2						
	Breast cancer deaths %	9.8	10.4	7.5	5.8	6.4	
	Multivariable HR (95% CI)	1.00 (Reference)	1.01 (0.66–1.55)	0.81 (0.38–1.72)	0.44 (0.21–0.93)	0.52 (0.26–1.06)	0.01
		Physical activity (MET-h/wk)					*P* value for interaction
		<9			≥9		
	Positive ER and PR						
	Breast cancer deaths %	10.4			6.2		
	Multivariable HR (95% CI)	1.00 (Reference)			0.50 (0.34–0.74)		
	Negative ER and PR						
	Breast cancer deaths %	9.9			8.7		
	Multivariable HR (95% CI)	1.00 (Reference)			0.91 (0.43–1.96)		0.08
		Physical activity (MET-h/wk)					
		<3.0	3–8.9	9–14.9	15–23.9	≥24	
Irwin 2008 [11]							
	Total deaths						
	Multivariable HR (95% CI)	1.00 (Reference)	0.39 (0.16–0.95)	0.38 (0.11–1.28)	0.78 (0.33–1.84)	0.27 (0.08–0.94)	0.038

Table 2 continued

		Physical activity (MET-h/wk)			
		0	>0–8.9	≥9	
	Breast cancer deaths				
	No. (%)	8 (7.0)	13 (4.4)	9 (3.2)	
	Multivariable HR (95% CI)	1.00 (Reference)	0.72 (0.28–1.85)	0.65 (0.23–1.87)	0.46
	Total deaths				
	No. (%)	22 (19.3)	18 (6.1)	13 (4.7)	
	Multivariable HR (95% CI)	1.00 (Reference)	0.36 (0.17–0.73)	0.33 (0.15–0.73)	0.046
PA one year before diagnosis	Breast cancer deaths				
	No. (%)	62 (15.6)	29 (12.2)	24 (8.0)	
	Multivariable HR (95% CI)	1.00 (Reference)	1.31 (0.80–2.21)	0.83 (0.49–1.38)	0.27
Irwin 2008 [11]					
PA one year before diagnosis	Total deaths	88 (22.2)	43 (18.1)	33 (8.0)	
	Multivariable HR (95% CI)	1.00 (Reference)	1.14 (0.75–1.74)	0.69 (0.45–1.06)	0.045

		Physical activity (MET-h/wk)		*P* value for interaction
		0	>0	
	Positive ER			
	Total deaths %	20.9	4.1	
	Multivariable HR (95% CI)	1.00 (Reference)	0.20 (0.09–0.46)	
	Negative ER			
	Total deaths %	6.7	8.3	
	Multivariable HR (95% CI)	1.00 (Reference)	1.26 (0.15–11.0)	0.27
	BMI < 25 kg/m^2			
	Total deaths %	24.3	7.2	
	Multivariable HR (95% CI)	1.00 (Reference)	0.47 (0.19–1.14)	
	BMI > 25 kg/m^2			
	Total deaths %	16.9	3.9	
	Multivariable HR (95% CI)	1.00 (Reference)	0.31 (0.13–0.74)	0.40

		Physical activity (MET-h/wk)				*P* value for trend
		≤2.7	2.8–7.9	8.0–20.9	≥21.0	
Holick 2008 [9]	Breast cancer deaths					
	No. (%)	37 (3.4)	26 (2.4)	25 (2.1)	21 (1.9)	
	Multivariable HR (95% CI)	1.00 (Reference)	0.66 (0.39–1.13)	0.61 (0.36–1.05)	0.49 (0.27–0.89)	0.05
	Total deaths					
	No. (%)	185 (16.7)	117 (10.9)	72 (6.1)	62 (5.5)	
	Multivariable HR (95% CI)	1.00 (Reference)	0.59 (0.45–0.77)	0.53 (0.40–0.71)	0.44 (0.32–0.61)	<0.001

Table 2 continued

		Physical activity (MET-h/wk)				P value for interaction
		<8.0	≥8.0			
	BMI < 25 kg/m^2					
	Breast cancer deaths %	1.7	1.4			
	Multivariable HR (95% CI)	1.00 (Reference)	0.91 (0.39–2.13)			
	BMI > 25 kg/m^2					
	Breast cancer deaths %	3.4	2.4			
	Multivariable HR (95% CI)	1.00 (Reference)	0.63 (0.39–1.02)			0.59
		Moderate-vigorous physical activity (MET-h/wk)				P value for trend
		<5.3	5.3–<15	15–<27	≥27	
Sternfeld 2009 [14]	Breast cancer deaths					
	Multivariable HR (95% CI)	1.00 (Reference)	0.77 (0.44–1.34)	0.47 (0.24–0.91)	0.90 (0.51–1.58)	0.38
	Total deaths					
	Multivariable HR (95% CI)	1.00 (Reference)	0.71 (0.48–1.07)	0.58 (0.37–0.90)	0.74 (0.49–1.13)	0.06
	Breast cancer recurrence					
	Multivariable HR (95% CI)	1.00 (Reference)	0.73 (0.49–1.09)	0.75 (0.50–1.12)	1.00 (0.68–1.46)	0.95
	Positive ER/PR					
	Multivariable HR (95% CI) for total deaths	1.00 (Reference)	0.64 (0.38–1.06)	0.46 (0.26–0.79)	0.59 (0.34–1.04)	0.01
	ER and/or PR negative					
	Multivariable HR (95% CI) for total deaths	1.00 (Reference)	0.80 (0.41–1.54)	1.06 (0.56–2.00)	0.75 (0.36–1.59)	0.69
	BMI < 25 kg/m^2					
	Multivariable HR (95% CI) for total deaths	1.00 (Reference)	0.52 (0.25–1.10)	0.42 (0.20–0.90)	0.38 (0.17–0.85)	0.01
	BMI 25–29.9 kg/m^2					
	Multivariable HR (95% CI) for total deaths	1.00 (Reference)	0.73 (0.37–1.43)	0.74 (0.38–1.45)	0.95 (0.47–1.94)	0.78
	BMI ≥ 30 kg/m^2					
	Multivariable HR (95% CI) for total deaths	1.00 (Reference)	0.84 (0.42–1.70)	0.89 (0.42–1.85)	0.90 (0.38–2.16)	0.76

Table 2 continued

		Selected physical activity (MET-h/wk)		
		<9	≥9	
	Breast cancer deaths			
	Multivariable HR (95% CI)	1.00 (Reference)	1.19 (0.78–1.84)	NS
	Total deaths			
	Multivariable HR (95% CI)	1.00 (Reference)	0.98 (0.71–1.35)	NS
	Breast cancer recurrence			
	Multivariable HR (95% CI)	1.00 (Reference)	1.16 (0.87–1.55)	NS

		Moderate-vigorous physical activity year before diagnosis (relative units)				*P* value for trend
		<16.6	16.7–29.4	29.5–43.0	≥43.1	
Abrahamson [8]						
PA one year before diagnosis	Total deaths					
	No. (%)	78 (22)	48 (16)	44 (14)	42 (16)	
	Multivariable HR (95% CI)	1.00 (Reference)	0.81 (0.57–1.17)	0.72 (0.49–1.04)	0.79 (0.54–1.15)	0.12

		Moderate-vigorous physical activity year before diagnosis (relative units)		
		Low	High	
Abrahamson [8]				
PA one year before diagnosis	BMI < 25 kg/m^2			
	Multivariable HR (95% CI) for total deaths	1.00 (Reference)	1.08 (0.77–1.52)	
PA one year before diagnosis	BMI ≥ 25 kg/m^2			
	Multivariable HR (95% CI) for total deaths	1.00 (Reference)	0.70 (0.49–0.99)	0.05

		Average physical activity year before diagnosis (h/w)			
		0	1–4	>5	
Enger [13]	Breast cancer deaths				
	No. (%)	143 (35)	15 (26)	15 (25)	
	Multivariable HR (95% CI)	1.00 (Reference)	0.85 (0.50–1.45)	0.78 (0.45–1.34)	0.31

Study or Subgroup	log[]	SE	Weight	IV, Fixed, 95% CI
1.1.1 Intermediate				
Enger 2004	-0.163	0.272	24.3%	0.85 [0.50, 1.45]
Irwin 2008	0.27	0.259	26.8%	1.31 [0.79, 2.18]
Subtotal (95% CI)			**51.0%**	**1.07 [0.74, 1.54]**
Heterogeneity: Chi² = 1.33, df = 1 (P = 0.25); I² = 25%				
Test for overall effect: Z = 0.34 (P = 0.73)				
1.1.2 Intermediate-High				
Enger 2004	-0.248	0.278	23.2%	0.78 [0.45, 1.35]
Irwin 2008	-0.186	0.264	25.8%	0.83 [0.49, 1.39]
Subtotal (95% CI)			**49.0%**	**0.81 [0.55, 1.17]**
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%				
Test for overall effect: Z = 1.13 (P = 0.26)				
Total (95% CI)			**100.0%**	**0.93 [0.72, 1.21]**
Heterogeneity: Chi² = 2.44, df = 3 (P = 0.49); I² = 0%				
Test for overall effect: Z = 0.54 (P = 0.59)				
Test for subgroup differences: Chi² = 1.09, df = 1 (P = 0.30), I² = 8.0%				

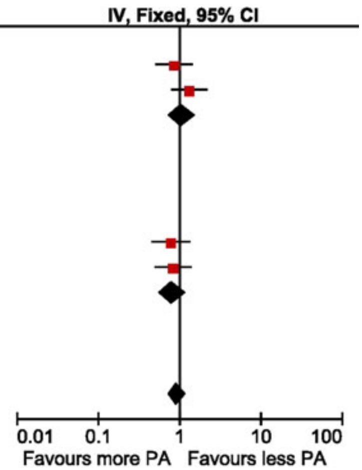


Fig. 1 Summary statistics and corresponding Forest plot for effect of pre-diagnosis physical activity on the hazard ratio of breast cancer mortality (Fixed-effects model)

Study or Subgroup	log[]	SE	Weight	IV, Fixed, 95% CI
1.2.2 Intermediate				
Abrahamson 2006	-0.211	0.183	30.0%	0.81 [0.57, 1.16]
Irwin 2008	0.131	0.215	21.7%	1.14 [0.75, 1.74]
Subtotal (95% CI)			**51.8%**	**0.93 [0.71, 1.23]**
Heterogeneity: Chi² = 1.47, df = 1 (P = 0.23); I² = 32%				
Test for overall effect: Z = 0.48 (P = 0.63)				
1.2.3 Intermediate-HighPA High				
Abrahamson 2006	-0.329	0.192	27.3%	0.72 [0.49, 1.05]
Irwin 2008	-0.371	0.219	21.0%	0.69 [0.45, 1.06]
Subtotal (95% CI)			**48.2%**	**0.71 [0.53, 0.94]**
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%				
Test for overall effect: Z = 2.41 (P = 0.02)				
Total (95% CI)			**100.0%**	**0.82 [0.67, 0.99]**
Heterogeneity: Chi² = 3.43, df = 3 (P = 0.33); I² = 13%				
Test for overall effect: Z = 2.02 (P = 0.04)				
Test for subgroup differences: Chi² = 1.95, df = 1 (P = 0.16), I² = 48.6%				

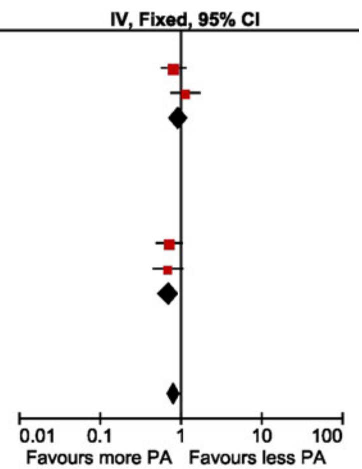


Fig. 2 Summary statistics and corresponding Forest plot for effect of pre-diagnosis physical activity on the hazard ratio of all causes mortality (Fixed-effects model)

overlaps in the classifications used in the studies. Moreover, in three studies [8, 10, 14], patients in groups with the highest level of physical activity did not demonstrate significantly different outcome when compared with those assigned to a physical activity level that was just lower (Table 2). Therefore, for the purpose of this meta-analysis, we considered different levels of physical activity according to the following: low-level physical activity (L-PA), 0 to ≤ 3 MET-h/wk; intermediate (I-PA), 2.8 to <8.9 MET-h/wk; intermediate to high-level physical activity (IH-PA), ≥8 MET-h/wk, and high-level physical activity (H-PA), ≥15 MET-h/wk. The minimal overlap in that classification was necessary to be able to include and analyze the available data. In the study of Sternfeld et al. [14], the investigators have examined total physical activity and estimated moderate–vigorous activity in relative units that were calculated by assigning MET-h/wk for each activity. Patients were grouped according to the quartile (Q) values, thus we considered patients in Q1, Q2, Q3, and Q4 as assigned to L-PA, I-PA, IH-PA, and H-PA, respectively.

Physical activity prior to breast cancer diagnosis

Two studies examined the effect of physical activity prior to breast cancer diagnosis on breast cancer mortality [11, 13]. As shown in Fig. 1, neither I-PA nor IH-PA was associated with a protective effect and the total HR compared with the reference group (L-PA) was 0.93 (95% CI, 0.72–1.21, $P = 0.59$). On the other hand, two studies explored the protective role of physical activity prior to diagnosis on total mortality [8, 11]. As shown in Fig. 2, compared with the reference group (L-PA), IH-PA reduced overall mortality by 29% (HR = 0.71, 95% CI, 0.53–0.94, $P = 0.02$); however, the total effect only suggested a potential benefit (HR = 0.82, 95% CI, 0.66–1.01, $P = 0.06$).

Physical activity after breast cancer diagnosis

When compared with the reference group (L-PA), all levels of post-diagnosis physical activity significantly reduced the

Fig. 3 Summary statistics and corresponding Forest plot for effect of post-diagnosis physical activity on the hazard ratio of breast cancer mortality (Fixed-effects model)

Study or Subgroup	log[]	SE	Weight	IV, Fixed, 95% CI	Year
3.1.1 Intermediate					
Holmes 2005	-0.223	0.145	28.5%	0.80 [0.60, 1.06]	2005
Irwin 2008	-0.329	0.482	2.6%	0.72 [0.28, 1.85]	2008
Holick 2008	-0.416	0.271	8.1%	0.66 [0.39, 1.12]	2008
Sternfeld 2009	-0.261	0.284	7.4%	0.77 [0.44, 1.34]	2009
Subtotal (95% CI)			**46.6%**	**0.76 [0.61, 0.95]**	
Heterogeneity: Chi² = 0.41, df = 3 (P = 0.94); I² = 0%					
Test for overall effect: Z = 2.37 (P = 0.02)					
3.1.2 Intermediate-High					
Holmes 2005	-0.693	0.248	9.7%	0.50 [0.31, 0.81]	2005
Holick 2008	-0.494	0.273	8.0%	0.61 [0.36, 1.04]	2008
Irwin 2008	-0.431	0.535	2.1%	0.65 [0.23, 1.85]	2008
Sternfeld 2009	-0.755	0.34	5.2%	0.47 [0.24, 0.92]	2009
Subtotal (95% CI)			**25.0%**	**0.54 [0.40, 0.73]**	
Heterogeneity: Chi² = 0.58, df = 3 (P = 0.90); I² = 0%					
Test for overall effect: Z = 4.01 (P < 0.0001)					
3.1.3 High					
Holmes 2005	-0.58	0.202	14.7%	0.56 [0.38, 0.83]	2005
Holick 2008	-0.713	0.304	6.5%	0.49 [0.27, 0.89]	2008
Sternfeld 2009	-0.105	0.288	7.2%	0.90 [0.51, 1.58]	2009
Subtotal (95% CI)			**28.4%**	**0.61 [0.46, 0.81]**	
Heterogeneity: Chi² = 2.52, df = 2 (P = 0.28); I² = 21%					
Test for overall effect: Z = 3.37 (P = 0.0008)					
Total (95% CI)			**100.0%**	**0.66 [0.57, 0.77]**	
Heterogeneity: Chi² = 7.20, df = 10 (P = 0.71); I² = 0%					
Test for overall effect: Z = 5.42 (P < 0.00001)					
Test for subgroup differences: Chi² = 3.69, df = 2 (P = 0.16), I² = 45.8%					

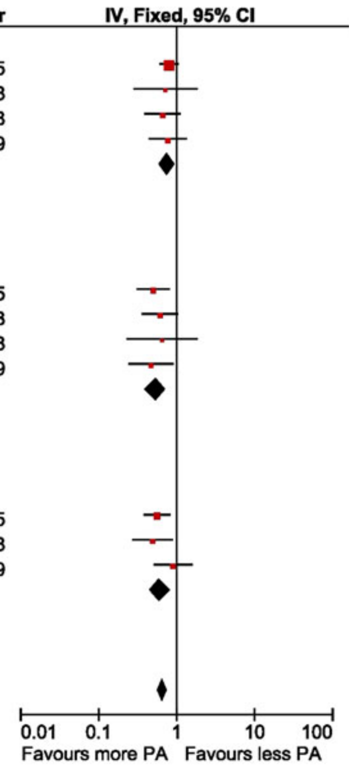
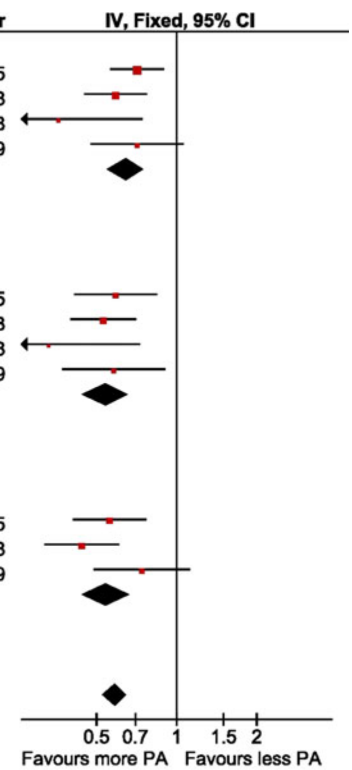


Fig. 4 Summary statistics and corresponding Forest plot for effect of post-diagnosis physical activity on the hazard ratio of all causes cancer mortality (Fixed-effects model)

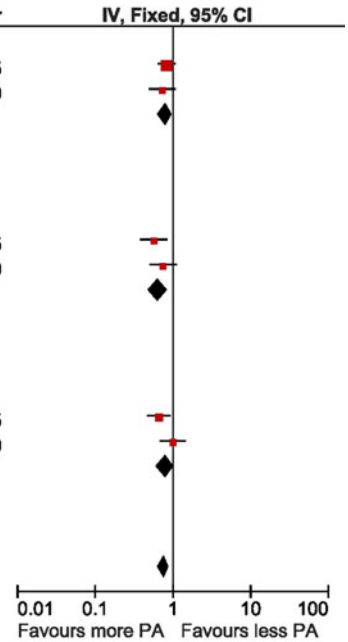
Study or Subgroup	log[]	SE	Weight	IV, Fixed, 95% CI	Year
3.2.2 PA Intermediate					
Holmes 2005	-0.342	0.118	20.2%	0.71 [0.56, 0.90]	2005
Holick 2008	-0.528	0.137	15.0%	0.59 [0.45, 0.77]	2008
Irwin 2008	-1.022	0.372	2.0%	0.36 [0.17, 0.75]	2008
Sternfeld 2009	-0.342	0.205	6.7%	0.71 [0.48, 1.06]	2009
Subtotal (95% CI)			**43.9%**	**0.65 [0.55, 0.76]**	
Heterogeneity: Chi² = 3.78, df = 3 (P = 0.29); I² = 21%					
Test for overall effect: Z = 5.46 (P < 0.00001)					
3.2.3 Intermediate-High					
Holmes 2005	-0.528	0.183	8.4%	0.59 [0.41, 0.84]	2005
Holick 2008	-0.635	0.146	13.2%	0.53 [0.40, 0.71]	2008
Irwin 2008	-1.109	0.404	1.7%	0.33 [0.15, 0.73]	2008
Sternfeld 2009	-0.545	0.227	5.5%	0.58 [0.37, 0.90]	2009
Subtotal (95% CI)			**28.8%**	**0.54 [0.45, 0.66]**	
Heterogeneity: Chi² = 1.84, df = 3 (P = 0.61); I² = 0%					
Test for overall effect: Z = 6.22 (P < 0.00001)					
3.2.4 High					
Holmes 2005	-0.58	0.161	10.8%	0.56 [0.41, 0.77]	2005
Holick 2008	-0.821	0.165	10.3%	0.44 [0.32, 0.61]	2008
Sternfeld 2009	-0.301	0.213	6.2%	0.74 [0.49, 1.12]	2009
Subtotal (95% CI)			**27.4%**	**0.54 [0.45, 0.66]**	
Heterogeneity: Chi² = 3.77, df = 2 (P = 0.15); I² = 47%					
Test for overall effect: Z = 6.00 (P < 0.00001)					
Total (95% CI)			**100.0%**	**0.59 [0.53, 0.65]**	
Heterogeneity: Chi² = 12.06, df = 10 (P = 0.28); I² = 17%					
Test for overall effect: Z = 10.09 (P < 0.00001)					
Test for subgroup differences: Chi² = 2.67, df = 2 (P = 0.26), I² = 25.2%					



risk of dying of breast cancer (Fig. 3). The total effect suggested a 34% reduction in breast cancer mortality (HR = 0.66, 95% CI, 0.57–0.77, $P < 0.00001$). Examining the potential association of post-diagnosis physical activity categorized according to the ranges of MET-h/wk as exactly reported in three studies [9–11], yielded an almost identical positive effect (HR = 0.62, 95% CI, 0.55–0.70, $P < 0.00001$).

Fig. 5 Summary statistics and corresponding Forest plot for effect of post-diagnosis physical activity on the hazard ratio of breast cancer recurrence (Fixed-effects model)

Study or Subgroup	log[]	SE	Weight	IV, Fixed, 95% CI	Year
3.3.2 Intermediate					
Holmes 2005	-0.186	0.133	30.2%	0.83 [0.64, 1.08]	2005
Sternfeld 2009	-0.315	0.204	12.8%	0.73 [0.49, 1.09]	2009
Subtotal (95% CI)			**43.0%**	**0.80 [0.64, 0.99]**	
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%					
Test for overall effect: Z = 2.01 (P = 0.04)					
3.3.3 Intermediate-High					
Holmes 2005	-0.562	0.205	12.7%	0.57 [0.38, 0.85]	2005
Sternfeld 2009	-0.288	0.206	12.6%	0.75 [0.50, 1.12]	2009
Subtotal (95% CI)			**25.3%**	**0.65 [0.49, 0.87]**	
Heterogeneity: Chi² = 0.89, df = 1 (P = 0.35); I² = 0%					
Test for overall effect: Z = 2.93 (P = 0.003)					
3.3.4 High					
Holmes 2005	-0.416	0.174	17.6%	0.66 [0.47, 0.93]	2005
Sternfeld 2009	0	0.195	14.0%	1.00 [0.68, 1.47]	2009
Subtotal (95% CI)			**31.7%**	**0.79 [0.62, 1.02]**	
Heterogeneity: Chi² = 2.53, df = 1 (P = 0.11); I² = 61%					
Test for overall effect: Z = 1.78 (P = 0.07)					
Total (95% CI)			**100.0%**	**0.76 [0.66, 0.87]**	
Heterogeneity: Chi² = 5.09, df = 5 (P = 0.40); I² = 2%					
Test for overall effect: Z = 3.80 (P = 0.0001)					
Test for subgroup differences: Chi² = 1.39, df = 2 (P = 0.50), I² = 0%					



Similarly, post-diagnosis physical activity showed 41% reduction in all causes mortality (HR = 0.59, 95% CI, 0.53–0.65, $P < 0.00001$). The benefit was demonstrated for all levels of physical activity (Fig. 4).

Moreover, I-PA and IH-PA, but not H-PA, reduced the likelihood breast cancer recurrence. The overall effect was highly significant (HR = 0.76, 95% CI, 0.66–0.87, $P = 0.00001$) (Fig. 5).

Interactions between physical activity, BMI, and mortality

All levels of physical activity prior to diagnosis reduced breast cancer mortality for those patients with BMI < 25 kg/m^2 (HR = 0.58, 95% CI, 0.46–0.75, $P < 0.0001$); however, it had insignificant effect on those with BMI ≥ 25 kg/m^2 (HR = 0.75, 95% CI, 0.56–1.02, $P = 0.07$). Nevertheless, these data were only available from a single study [10].

In two studies [9, 11], post-diagnosis physical activity (more vs. less) reduced breast cancer deaths among those with BMI ≥ 25 kg/m^2 (HR = 0.53, 95% CI, 0.35–0.81, $P = 0.003$) but had no effect on those with BMI < 25 kg/m^2 (Fig. 7). On the other hand, in two studies [11, 14], post-diagnosis physical activity (more vs. less) reduced all causes mortality regardless of the BMI (Fig. 6).

Interactions between physical activity, estrogen receptor (ER) status, and mortality. In the two studies that examined the effect of post-diagnosis physical activity on all causes mortality adjusted for ER status [11, 14], there was a suggested benefit for those with ER-positive tumors (HR = 0.36, 95% CI, 0.12–1.03, $P = 0.06$); however, patients with ER-negative tumors gained no benefit (Fig. 7). Only one study examined the association between post-diagnosis physical activity and breast cancer mortality adjusted for ER status [10]. The study showed a beneficial effect among those with ER-positive tumors (HR = 0.50, 95% CI, 0.34–0.74, $P = 0.0005$), but not for patients with negative ER (HR = 0.91, 95% CI, 0.43–1.94, $P = 0.81$).

Discussion

This meta-analysis that included 12,108 women with invasive breast cancer elucidated the potential effect of physical activity on breast cancer outcome. While, physical activity prior to breast cancer diagnosis had no effect on the disease-specific deaths, nevertheless, pre-diagnosis physical activity appeared to reduce breast cancer mortality among those with BMI < 25 kg/m^2. Moreover, pre-diagnosis physical activity (IH-PA) significantly reduced all causes mortality by 18%. One plausible explanation of the modest effect of pre-diagnosis physical activity may be related to the fact that 24–50% of patients with breast cancer reported decreased in post-diagnosis compared to pre-diagnosis physical activity [20].

On the other hand, the potential benefit of post-diagnosis physical activity was more convincing. All levels of post-diagnosis physical activity reduced breast cancer mortality by approximately 30% and decreased all causes mortality by 41%. In contrast to the effect of physical activity prior to breast cancer diagnosis vs. BMI, post-diagnosis physical

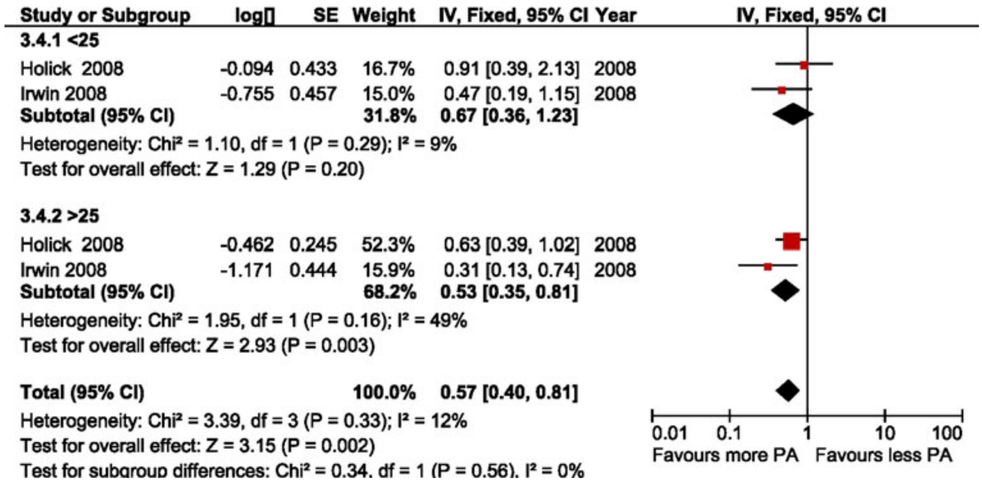


Fig. 6 Summary statistics and corresponding Forest plot for effect of post-diagnosis physical activity on the hazard ratio of all causes mortality according to patients' BMI (Fixed-effects model)

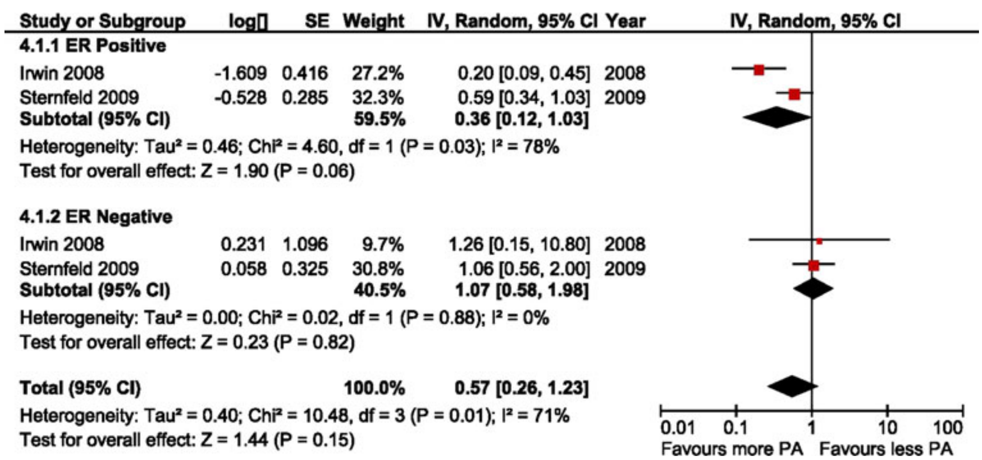


Fig. 7 Summary statistics and corresponding Forest plot for effect of post-diagnosis physical activity on the hazard ratio of all causes mortality according to ER status (Random-effects model)

activity only benefitted obese women with BMI $\geq$ 25 kg/m^2 with a reduction of breast cancer deaths by 47%, whereas pre-diagnosis physical activity reduced breast cancer mortality for those with BMI < 25 kg/m^2. Additionally, post-diagnosis physical activity reduced all causes mortality regardless of the BMI. There is a large body of evidence that increasing BMI or weight is associated with poorer breast cancer outcome [21].

Analysis of the impact of post-diagnosis physical activity on breast cancer outcome adjusted for ER receptor status revealed interesting, albeit, expected findings. Physical activity was shown to reduce all causes and disease-specific mortality by 64 and 50%, respectively, only for women with ER-positive tumors. On the other hand, no benefit was shown among women with ER-negative disease. The inverse association between physical activity and mortality particularly among patients with ER-positive disease is potentially attributed to the beneficial effect of exercise on estrogen levels [22].

The exact mechanisms of the protective role of physical activity on breast cancer mortality have been debated. It is conceivable that physical activity may be associated with breast cancer outcome by the same mechanisms that are proposed to affect etiology. These include decreased lifetime estrogen exposure, augmented immune function, and lower body fat [23–25]. Equally important is the effect of physical activity in patients with breast cancer on the cardiovascular disease risk profile such as lower C-reactive protein and lower blood pressure [26]. Another proposed hypothesis is related to insulin resistance [26]. It has been postulated that chronically elevated insulin level is associated with breast cancer [27], and it is known that obesity [28] and physical inactivity [29] are two of the main environmental determinants of insulin resistance.

However, the Oslo Trial reported that exercise alone did not significantly improve insulin resistance although diet alone, or diet and exercise did result in improvement [30]. On the other hand, Borugian et al. have shown—only in post-menopausal women—that high levels of insulin were associated with poorer survival [19].

Results of this meta-analysis, however, may have several limitations. First, the meta-analysis was based on published reports rather than on individual patient data (IPD). However, it is known that the most frequent type of meta-analysis that is published in literature now is based on summary data that is abstracted from actual research papers [31]. IPD meta-analyses are more costly and time-intense. Moreover, in oncology literature there are many reports that have shown a strong concordance between the two methods.

Second, included studies have used different cutoff points to group patients according to their physical activity as measured in MET-h/wk. Nevertheless, we have attempted comparisons that allow minimal overlaps. Using sensitivity analysis to address potential misclassification of physical activity exposure, Abrahamson et al. reported that the beneficial impact of physical activity may be even stronger [8]. Moreover, in some of the studies that included extreme levels of vigorous physical activity, there was very little or no evidence of an added benefit [14]. Third, different studies have used different definitions for the measured physical activity (Table 1). The latter disadvantage may certainly preclude providing solid recommendation about the appropriate level of physical activity that may be associated with potential breast cancer benefit. Nevertheless, it seems that there is no evidence of dose–response relation between physical activity and potential benefit [19].

Fourth, early breast cancer symptoms prior to diagnosis may alter patients' behavior. Moreover, for post-diagnosis physical activity, it is possible that the sickest patients are the ones who are unable to exercise and more likely to die. However, all reported outcomes in this meta-analysis have been adjusted for known prognostic variables such as age and stage. Besides, all the included studies excluded stage IV patients. Additionally, the relatively short interval between diagnosis and inclusion may have minimized any bias of selective survival.

Fifth, the included studies may have not accounted for other confounding risk modifiers such as diet or for potential socioeconomic factors such as access to quality care. However, the consistent positive results for most of the measured effects suggest that the influence of the confounders may have been minimal. Moreover, the lack of beneficial effects for certain groups presents further support to the validity of the derived conclusions.

Sixth, physical activity in all included studies was self-reported. In one of the largest study included, a similar association was reported between physical activity and other illnesses and that supports the reliability of physical activity's assessment [10]. However, we acknowledge that self-reporting may certainly introduce recall error that may have biased the results [32].

Despite those limitations, the current meta-analysis has much strength. First, it represents the only attempt for a comprehensive systematic analysis intended to study the impact of physical activity on breast cancer survival. Second, the meta-analysis included a large patient population. Third, the analysis addressed several important issues including the effect of pre-diagnosis and post-diagnosis physical activity, the effect on breast cancer and all causes mortality, the effect on breast cancer recurrence, the relation between physical activity and BMI, and the association between physical activity and ER status of the disease.

In conclusion, the current meta-analysis provides supporting evidence for a beneficial effect of physical activity on breast cancer outcome. The results are encouraging and it showed that physical activity being relatively convenient, easy, and affordable risk modifier that may be able to change breast cancer outcome for millions of women. The demonstrated benefits may be equal or higher than most of the currently available interventions. Future research should include more thorough and comprehensive assessment of lifetime physical activity; furthermore, internationally accepted and uniform definitions of physical activity are required. Only then, we could better determine the level of activity that may be associated with most benefit also we would be able to compare between studies.

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