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Physical activity and risk of breast cancer: a meta-analysis of prospective studies

Yili Wu · Dongfeng Zhang · Shan Kang

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Abstract We conducted a meta-analysis to summarize the evidence from prospective studies regarding the association between physical activity and breast cancer risk. A comprehensive search was conducted to identify eligible studies. The fixed or random effect model was used based on heterogeneity test. The dose–response relationship was assessed by restricted cubic spline model and multivariate random-effect meta-regression. Overall, 31 studies with 63,786 cases were included, and the combined relative risk (RR) with 95 % CI of breast cancer was 0.88 (0.85–0.91). In subgroup analysis by activity type, data from 27 studies including 37,568 cases for non-occupational activity (including recreational activity and household activity) and seven studies including 28,268 cases for occupational activity were used, and the RR (95 % CI) of breast cancer was 0.87 (0.83–0.91) and 0.90 (0.83–0.97), respectively. The inverse association was consistent among all subgroups analyses. Stronger association was found for subjects with BMI <25 kg/m^2 [0.72 (0.65–0.81)], premenopausal women [0.77 (0.72–0.84)], and estrogen and progesterone receptor-negative breast cancer [0.80 (0.73–0.87)]. Dose–response analysis suggested that the risk of breast cancer decreased by 2 % ($P < 0.00$) for every 25 metabolic equivalent (MET)-h/week increment in non-occupational physical activity, 3 % ($P < 0.00$) for every 10 MET-h/week (roughly equivalent to 4 h/week of walking in 2 miles/h or 1 h/week of running in 6 miles/h) increment in recreational activity, and 5 % ($P < 0.00$) for every 2 h/week increment in moderate plus vigorous recreational activity, respectively. Physical activity could significantly reduce the risk of breast cancer.

Keywords Physical activity · Breast cancer · Meta-analysis

Introduction

Breast cancer ranks second as a cause of cancer death in women (after lung cancer), and an estimated 226,870 new cases of invasive breast cancer are expected to occur among women in the US during 2012 [1]. Although incremental improvements are made in earlier detection and medical therapies, the incidence rate of breast cancer is stable since 2004 [1]. The prevalence of inactivity in population was estimated to be 38.8 % [2] or 40.6 % [3] worldwide, and the adjusted population attributable fraction for breast cancer associated with physical inactivity was about 10 % [2, 3]. The American Cancer Society Guidelines suggested that adults should engage in at least 150 min of moderate intensity or 75 min of vigorous intensity activity each week, or an equivalent combination [4]. Physical activity has been hypothesized to protect against breast cancer since 1980s [5], and over 80 studies have been conducted to assess the association between physical activity and breast cancer risk worldwide during the past 20 years [6]. A thorough review by Friedenreich et al. [6] is available to summarize the epidemiologic evidence on physical activity and breast cancer risk. However, no meta-analysis is available, and the dose–response relationship as well as the possibility that physical activity might have a threshold effect on breast cancer risk is still unclear. Besides, categories of physical activity levels differed between studies, which might complicate the

Y. Wu · D. Zhang (✉) · S. Kang
Department of Epidemiology and Health Statistics, The Medical College of Qingdao University, Dongzhou Road, No. 38, Qingdao 266021, Shandong, People's Republic of China
e-mail: zhangdf1962@yahoo.com.cn

interpretation of the pooled results across study populations with different categories. In this respect, a dose–response meta-analysis with restricted cubic spline functions provides a solution to the problem [7] from which a summary risk estimate can be derived for a standardized increment and specific exposure values for physical activity levels. Prospective studies do not suffer from recall bias and are anticipated to be less likely to have selection bias relative to case–control studies. Therefore, we conducted a meta-analysis of prospective studies to (1) first assess the breast cancer risk for the highest vs. lowest categories of physical activity; (2) then evaluate the possible dose–response relationship between physical activity and breast cancer risk; (3) evaluate the modification of key covariates to the association between physical activity and breast cancer risk; (4) and explore the heterogeneity among studies and publication bias.

Materials and methods

Literature search and selection

We performed a literature search up to Nov 2012 using the databases of Pubmed, ISI Web of Knowledge, and China Biology Medical literature database, using the following search terms: "physical activity", "breast cancer", and "cohort" without restrictions. Moreover, we reviewed the reference lists from retrieved articles to search for further relevant studies.

Two investigators independently reviewed all identified studies, and studies were included if they met the following criteria: (1) a prospective design; (2) the exposure of interest was physical activity; (3) the outcome of interest was breast cancer; (4) multivariate-adjusted relative risk (RR) with 95 % confidence interval (CI) was provided; (5) and for dose–response analysis, the number of cases and participants or person-years for each category of physical activity must be also provided (or data available to calculate them). If data were duplicated in more than one study, we included the study with the largest number of cases.

Data extraction

The following data were extracted from each study by two investigators: the first author's last name, publication year, follow-up duration, location where the study was performed, sample size and number of cases, type of physical activity, variables adjusted for in the analysis, RR estimates with corresponding 95 % CI for the highest versus lowest categories of physical activity, menopausal status (premenopausal and postmenopausal), estrogen receptor (ER) and progesterone receptor (PR) status (positive: ER+/PR+, or negative: ER−/PR−), category of BMI (>25 kg/m^2 or<25 kg/m^2), tumor stage (in situ or invasive), and the period of life during which physical activity was performed. For dose–response analysis, the number of cases and participants (person-years), and RR (95 % CI) for each category of physical activity were also extracted. The median or mean level of physical activity for each category was assigned to the corresponding RR for every study. If the upper boundary of the highest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category. We extracted the RRs that reflected the greatest degree of control for potential confounders. If available, we also extracted the age-adjusted RRs and multivariate-adjusted RRs without adjustment for body mass index (BMI).

Statistical analysis

Pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR with 95 % CI to assess the strength of association between physical activity and risk of breast cancer. The I^2 of Higgins and Thompson was used to assess heterogeneity (I^2 values of 0, 25, 50, and 75 % represent no, low, moderate, and high heterogeneity [8], respectively). The fixed effect model (FEM) was used as the pooling method if moderate or lower heterogeneity ($I^2 < 50$ %) was found; otherwise, the random effect model (REM) was adopted ($I^2 \geq 50$ %). The method proposed by Patsopoulos et al. [9] was used with $I^2 > 50$ % as the criterion to assess the influence of between-study heterogeneity on the combined results by reducing between-study heterogeneity. A sensitivity analysis was performed with one study removed at a time to assess whether the results could have been affected markedly by a single study [10]. Publication bias was evaluated using the Egger regression asymmetry test. Subgroup analysis was performed by type of physical activity categorized as occupational activity and non-occupational activity (including recreational activity and household activity), intensity of physical activity (moderate or vigorous), the period of life during which physical activity was performed [<25 year, 25–50 years, >50 years or, throughout the follow-up (updated information of physical activity was used)], menopausal status (premenopausal or postmenopausal), ER and PR status (ER+/PR+ or ER−/PR−), category of BMI (>25 kg/m^2 or <25 kg/m^2), tumor stage (in situ or invasive), follow-up duration (>10 years or <10 years), and location where the study was conducted (America, Europe, or Asia). According to the METs assigned to each specific activity [11], we combined the intensity of activity reported as "high", "active", "strenuous", or "vigorous" in the original studies as vigorous intensity.

A two-stage random-effects dose–response meta-analysis was performed taking into account the between-study heterogeneity proposed by Orsini et al. [12] to compute the trend from the correlated log RR estimates across levels of physical activity. Briefly, a restricted cubic spline model with three knots at the 25th, 50th, and 75th percentiles [13] of the levels of physical activity, was estimated using generalized least square regression taking into account the correlation within each set of published RRs [14]. Then the study-specific estimates were combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis [15]. A P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0. If a linear relationship was found, a summary risk estimate was derived for a standardized increment of non-occupational physical activity (25 MET-h/week), recreational activity (10 MET-h/week), and moderate plus vigorous recreational activity (2 h/week), respectively. All statistical analyses were performed with STATA version 12.0 (Stata Corporation, College Station, TX, USA). All reported probabilities (P values) were two-sided with $P < 0.05$ considered statistically significant.

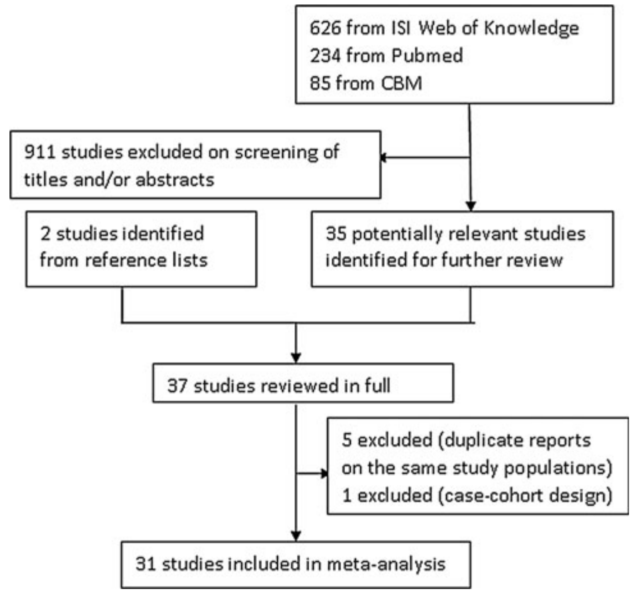

Fig. 1 Selection of studies for inclusion in this meta-analysis

Results

Literature search and study characteristics

The detailed steps of our literature search are shown in Fig. 1. Briefly, we identified 37 potentially relevant studies concerning physical activity and breast cancer risk, and two [16, 17] of the 37 studies were identified from reference lists. Five studies [18–22] were excluded because of duplicate reports from the same study population, and one study was also excluded because of a case–cohort design [23]. The remaining 31 prospective-design studies [16, 17, 24–52] were included in this meta-analysis. The detailed characteristics of the 31 studies are shown in Table 1.

Considering the dose–response analysis, only one study [50] provided the data for occupational activity; thus, we did not conduct the dose–response analysis for occupational activity. For non-occupational activity, three studies [42, 50, 52] provided the data for non-occupational activity overall (combining recreational activity and household activity) in MET-h/week, while one study [29] measured the non-occupational activity overall in kcal/week. Eleven studies [16, 24, 34, 37, 42, 45, 46, 49–52] (seven [24, 37, 42, 45, 49, 50, 52] in MET-h/week) provided the data for recreational activity. Because the value for combined results of recreational activity with household activity (the highest category >131.5 MET-h/week) was much higher than that of recreational activity (the highest category >54.0 MET-h/week), we only included the combined results in the dose–response analysis for non-occupational activity. Thus, data from three studies [42, 50, 52] were used in the dose–response analysis for non-occupational activity, and data from seven studies [24, 37, 42, 45, 49, 50, 52] were used in the dose–response analysis for recreational activity with MET-h/week as the measurement, respectively. Besides, ten studies [24, 28, 30, 41–45, 47, 49] (eight in h/week [24, 28, 30, 41–43, 45, 47]) provided the data that could be used for moderate plus vigorous activity; thus, we conducted a dose–response analysis for moderate plus vigorous activity using the data from the eight studies [24, 28, 30, 41–43, 45, 47] with h/week as the measurement. The type of moderate plus vigorous activity included in the dose–response was all recreational activity in the original studies.

Quantitative synthesis

The results are summarized in Table 2.

Overall association between physical activity and breast cancer risk

A total of 31 prospective studies were included involving 63,786 breast cancer cases. The combined RR (95 % CI) of breast cancer was 0.88 (0.85–0.91), $I^2 = 29.5$ % (Fig. 2). The association did not change materially considering age-adjusted model [16, 25–28, 30, 32, 35, 37, 41–44, 46–50] (RR = 0.85, 95 % CI = 0.79–0.90, $I^2 = 52.3$ %), multivariate-adjusted model without adjustment for BMI [16, 17, 25, 28, 34, 36, 39–41, 44, 45, 48, 50, 51] (RR = 0.89, 95 % CI = 0.85–0.93, $I^2 = 35.5$ %), and multivariate-adjusted

Table 1 Characteristics of prospective studies on physical activity and breast cancer

Author, year, [ref.]	Study name, age (years)	Follow - up (years)	Country	Sample size (no. cases)	PA type	RR (95 % CI) for highest versus lowest category of PA	Adjustment for covariates
Dorgan et al. 1994 [25]	The Framingham heart study, 35–68	28	USA	2,307 (117)	Total	PA index (4th vs. 1 th) 1.6 (0.9–2.9)	Age, number of pregnancies, menopausal status, age at first pregnancy, education, occupation, and alcohol ingestion
Thune et al. 1997 [26]	The national health screening service, 20–54	13.7	Norway	25,624 (351)	Recreational	Regular exercise versus sedentary 0.63 (0.42–0.95)	Age, BMI, height, county of residence, and number of children
					Occupational	Heavy versus sedentary 0.48 (0.25–0.92)	
Cerhan et al. 1998 [27]	The Iowa 65 + Rural health study, 65–102	21	USA	1,806 (46)	Non-occupational	High versus inactive 0.2 (0.05–1.0)	Age, education, BMI, age at menarche, age at menopause, HRT use, and systolic blood pressure.
Rockhill et al. 1998 [28]	The nurses' health study II, 25–42	6	USA	116,671 (372)	Moderate plus vigorous	≥7.0 versus <1 h/week 1.1 (0.8–1.5)	Age, age at menarche, history of benign breast disease, history of breast cancer in mother and/or sister, recent alcohol consumption, height, OC use, parity and age at first birth
Sesso et al. 1998 [29]	The college alumni Health Study, 37–69	32	USA	1,566 (109)	Non-occupational	>1000 versus <500 kcal/week 0.73 (0.46–1.14)	Age and BMI
Rockhill et al. 1999 [30]	The nurses's health study, 30–55	16	USA	121,701 (3,137)	Moderate plus vigorous	≥7.0 versus <1 h/wk 0.82 (0.70–0.97)	Age, age at menarche, history of benign breast disease, history of breast cancer in mother and/or sister, height, parity and age at first birth, BMI, menopausal status, and HRT use
Luoto et al. 2000 [31]	None, 15–64,	17	Finland	30,548 (332)	Recreational	Daily versus <once/week 1.01 (0.72–1.42)	Education, parity and age at first birth, number of children, and BMI
Wyrwich et al. 2000 [32]	The longitudinal study on aging, 70–98	8	USA	3131 (77)	Non-occupational	High versus inactive 0.43 (0.19–0.96)	Prior cancer, age, BMI and education
Breslow et al., 2001 [33]	The NHANES I, 24–75	9.2	USA	6,445 (138)	Recreational	High versus low 0.58 (0.31–1.07)	Height, BMI at age 25 years, adult weight change, and sample design variables
Lee et al. 2001 [34]	The women's health study, ≥45	2	USA	39,322 (411)	Non-occupational	≥6300 versus <840 kj/week 0.80 (0.58–1.12)	BMI, alcohol consumption, age at menarche, age at first pregnancy lasting ≥6 months, number of pregnancies lasting ≥6 months, menopausal status, OC use, HRT use, and family history of breast cancer

Table 1 continued

Author, year, [ref.]	Study name, age (years)	Follow - up (years)	Country	Sample size (no. cases)	PA type	RR (95 % CI) for highest versus lowest category of PA	Adjustment for covariates
Moradi et al. 2002 [35]	Swedish Twin Registry, 42–70	28	Sweden	9,539 (506)	Recreational	Regular activity versus sedentary 0.8 (0.6–1.2)	Age
					Occupational	Strenuous vs. sedentary 1.0 (0.7–1.5)	
Rintala et al. 2002 [36]	None, ≥25	26	Finland	680,000 (17,986)	Occupational	Heavy versus sitting/light tasks 0.74 (0.61–0.91)	Social class and reproductive factors
McTiernan et al. 2003 [24]	The WHI observational study, 50–79	4.7	USA	74,171 (1,780)	Recreational	>40 MET-h/week versus none 0.78 (0.62–1.00)	Age, BMI, HRT use, race, geographic region, income, education, ever breasted, hysterectomy status, first-degree relative with breast cancer, smoking status, parity, age at first birth, number of mammograms, alcohol use, age at menarche, and age at menopause
Patel et al. 2003 [37]	The CPS-II Nutrition Cohort, 50–74	5	USA	72,608 (1,520)	Recreational	>42 MET-h/week versus none 0.71 (0.49–1.02)	Age, race, BMI, weight change, family history of breast cancer, personal history of breast cysts, OC use, HRT use, parity, age at menarche, age at menopause, smoking, alcohol intake, caloric intake, education, and mammography history
Margolis et al. 2005 [38]	The women's lifestyle and health study, 30–49	9.1	Norway and Sweden	99,504 (1,166)	Non-occupational	Vigorous versus none 1.24 (0.85–1.82)	Age, years of education, BMI, height, smoking status, alcohol intake, age at menarche, parity, age at first birth, number of months of breast feeding, OC use, family history of breast cancer, menopausal status, and country of origin
Schnohr et al. 2005 [17]	The Copenhagen centre for prospective population studies, 20–93	14	Denmark	13,216 (417)	Recreational	Vigorous versus low 1.12 (0.83–1.53)	Age, birth cohort, cohort membership, occupational physical activity, smoking, education, alcohol, BMI and parity
Bardia et al. 2006 [39]	The Iowa women's health study, 55–69	18	USA	41,836 (2,548)	Non-occupational	High versus low 0.91 (0.82–1.01)	Age, educational level, family history of breast cancer, age at menarche, number of live births, age at first live birth, OC use, age at menopause, HRT use, alcohol, smoking, and BMI

Table 1 continued

Author, year, [ref.]	Study name, age (years)	Follow - up (years)	Country	Sample size (no. cases)	PA type	RR (95 % CI) for highest versus lowest category of PA	Adjustment for covariates
Chang et al. 2006 [16]	The PLCO cancer screening trial 55–74	11	USA	38,660 (764)	Recreational	≥4 versus 0 h/week 0.81 (0.63–1.05)	Study center, race, height, family history of breast cancer, history of benign breast disease, age at menarche, age at first birth, parity, age at menopause, HRT use, education, energy intake, and BMI
Mertens et al. 2006 [40]	The ARIC study, 45–64	13.1	USA	7994 (342)	Non-occupational	PA index (4th vs. 1th)1.16 (0.86–1.56)	Age, race, center, age at first live birth, age at menopause, and family history of breast cancer in one first-degree relative.
					Occupational	PA index (4th vs. 1th) 0.87 (0.61–1.24)	
Silvera et al. 2006 [41]	The NBSS, 40–59	16.4	Canada	40,318 (1,673)	Vigorous	>60 versus <30 min/day 0.93 (0.78–1.10)	Age, alcohol, smoking history, OC use, HRT use, parity, age at menarche, age at first live birth, family history of breast cancer, history of breast disease, menopausal status, study center, randomization group, energy intake, and BMI
Tehard et al. 2006 [42]	The E3 N Cohort study, 40–65	13	France	90,509 (3,424)	Non-occupational	≥57.8 versus <28.3 MET-h/week 0.90 (0.80–1.02)	BMI, menopausal status, HRT use, age at menarche, age at first full-term pregnancy, parity, marital status, OC use, first-degree family history of breast, personal history of benign breast disease, and employed
Dallal et al. 2007 [43]	The California teachers study, 20–79	6.6	USA	110,599 (2,649)	Moderate plus vigorous	>5 versus <0.5 h/week 0.87 (0.74–1.02)	Race, family history of breast cancer, age at first full-term pregnancy and number of full-term pregnancies combined variable, HRT and menopausal status combined variable, BMI, smoking, alcohol, history of breast biopsy, and mammography screening
Leitzmann et al. 2008 [44]	The BCDDP study, >60	12	USA	32,269 (1,506)	Total	395–721 versus 105–244 MET-h/week 0.87 (0.74–1.02)	Age, family history of breast cancer, history of benign breast disease, breast cancer screening history, height, age at menarche, age at menopause, age at first live birth, HRT use, education attainment, smoking, and intakes of energy-adjusted dietary fat, alcohol and BMI

Table 1 continued

Author, year, [ref.]	Study name, age (years)	Follow - up (years)	Country	Sample size (no. cases)	PA type	RR (95 % CI) for highest versus lowest category of PA	Adjustment for covariates
Maruti et al. 2008 [45]	The nurses' health study II, 25–42	6	USA	64,777 (550)	Non-occupational	≥54.0 versus <21.0 MET-h/week 0.77 (0.59–1.01)	Age, average childhood body shape, history of benign breast disease, mother or sister with breast cancer, parity and age at first birth, alcohol, and height
Suzuki et al. 2008 [46]	The Japan collabora-tive cohort study, 40–69	12.4	Japan	30,157 (207)	Recreational	Time spent walking (≥1 h/day)/exercising (≥1 h/week) versus <1 h/day/<1 h/week) 0.45 (0.25–0.78)	Age, BMI, alcohol, age at menarche, education level, parity, age at birth of first child, HRT use, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age
Howard et al. 2009 [47]	The U.S. radiologic technologists cohort, mean: 46.5	8.9	USA	45,631 (864)	Total	≥97 versus <9.5 MET-h/week 0.91 (0.74–1.13)	Age, BMI, age at menarche, parity, age at first birth, age at menopause, family history of breast cancer, personal history of breast disease, OC use, HRT use, race, smoking, and alcohol
Peters et al. 2009 [48]	The NIH-AARP diet and health study, 50–71	7	USA	182,862 (6,609)	Total	≥ 5 versus <1 times/week 0.92 (0.85–1.00)	Age, race, education level, smoking, family history of breast cancer, HRT use, age at first birth, age at menarche, age at menopause, parity, alcohol and BMI
Eliassen et al. 2010 [49]	The nurses' health study, 54–65	20	USA	95,396 (4,782)	Recreational	≥27 versus <3 MET-h/week 0.88 (0.79–0.98)	Age at menarche, BMI at 18 years, height, parity and age at first birth, alcohol, HRT use, age at menopause, missing age at menopause, family history of breast cancer, and history of benign breast disease
Pronk et al. 2011 [50]	The SWHS, 40–70	9.0	China	73,049 (717)	Non-occupational	>131.5 versus <74.3 h/week 0.98 (0.79–1.21)	Age, education, family history of breast cancer, age at first birth, and number of pregnancies
					Occupational	≥10.00 versus 4.64 kj/min 0.73 (0.53–0.99)	
Suzuki et al. 2011 [51]	The JPHC study, 40–69	14.5	Japan	53,578 (652)	Recreational	≥3 days/week versus ≤3 days/month	Age, area, height, BMI, smoking, age at menarche, age at first birth, parity, age at menopause, HRT use, alcohol, and energy-adjusted intake of isoflavones
					Total	0.73 (0.54–1.00) METs/day score (tertile 3 vs. tertile 1) 1.03 (0.75–1.41)	

Table 1 continued

Author, year, [ref.]	Study name, age (years)	Follow-up (years)	Country	Sample size (no. cases)	PA type	RR (95 % CI) for highest versus lowest category of PA	Adjustment for covariates
Steindorf et al. 2012 [52]	The EPIC-cohort study, 20–98.5	11.6	Europe	257,805 (8,034)	Non-occupational	>123 versus <50.5 MET-h/week 0.87 (0.81–0.94)	BMI, age at first period, age at first full term pregnancy, number of full term pregnancies, breast feeding, OC use, menopausal status, age at menopause, HRT use, alcohol, smoking, level of school attained, and other types of physical activity
					Occupational	Manual/heavy manual versus sedentary 0.96 (0.88–1.06)	
					Total	Active versus inactive 0.87 (0.79–0.97)	

BMI body mass index, *HRT* hormone replacement therapy, *OC* oral contraceptives, *PA* physical activity

model with adjustment for BMI [16, 24, 26, 27, 29–34, 37–39, 41–44, 46–49, 51, 52] (RR = 0.88, 95 % CI = 0.85–0.91, $I^2 = 23.0$ %).

Considering the follow-up duration, the combined result was 0.89 (0.84–0.94, $I^2 = 29.3$ %) (<10 years [24, 28, 32–34, 37, 38, 43, 45, 47, 48, 50]) and 0.88 (0.84–0.91, $I^2 = 32.3$ %) (>10 years [16, 17, 25–27, 29–31, 35, 36, 39–42, 44, 46, 49, 51, 52]), respectively.

Low or moderate between-study heterogeneity ($I^2 <$ 50 %) was found in all analyses except for the analysis in age-adjusted model ($I^2 = 52.3$ %), and the result did not change materially (RR = 0.89, 95 % CI = 0.85–0.92, $I^2 = 41.5$ %) using $I^2 > 50$ % as the criterion to reduce between-study heterogeneity after excluding the result for occupational activity in one study [50].

Type and intensity of physical activity

Similar result was found for breast cancer risk with occupational activity [26, 31, 35, 36, 40, 50, 52] (RR = 0.90, 95 % CI = 0.83–0.97, $I^2 = 46.1$ %) and non-occupational activity [16, 17, 24, 26–35, 37–43, 45–47, 49–52] (RR = 0.87, 95 % CI = 0.84–0.91, $I^2 = 27.7$ %). Non-occupational activity included recreational activity and household activity, and similar result was found for breast cancer risk with recreational activity [16, 17, 24, 26, 28–35, 37–43, 45–47, 49, 51, 52] (RR = 0.89, 95 % CI = 0.85–0.92, $I^2 = 25.7$ %) and household activity [42, 50, 52] (RR = 0.89, 95 % CI = 0.83–0.95, $I^2 = 0.00$ %). Besides, similar result was found between breast cancer risk and walking (a subtype of recreational activity) [RR = 0.88, 95 % CI = 0.81–0.96, $I^2 = 7.90$ %] [42, 45–47, 50].

Considering intensity of physical activity, stronger association was found between breast cancer risk and vigorous activity [16, 17, 24, 26–28, 30, 32, 33, 35–39, 41–45, 47, 52] (RR = 0.86, 95 % CI = 0.82–0.89, $I^2 = 32.9$ %) than that and moderate activity [17, 26, 27, 32, 33, 35–39, 42–45, 47, 52] (RR = 0.97, 95 % CI = 0.94–0.99, $I^2 = 27.2$ %). Low or moderate between-study heterogeneity ($I^2 < 50$ %) was found in all analyses.

Population subgroups

The inverse association between physical activity and breast cancer risk was observed across different population subgroups by location where the study was conducted (America [16, 24, 25, 27–30, 32–34, 37, 39–41, 43–45, 47–49], Europe [17, 26, 31, 35, 36, 38, 42, 52], or Asia [46, 50, 51]), menopausal status (premenopausal [26, 41, 45–47, 51] or postmenopausal [16, 24, 26, 27, 29, 32, 34, 36, 37, 39, 41, 44, 46–49, 51]), BMI (<25 kg/m^2 [24, 29, 31, 35, 37, 43–46] or >25 kg/m^2 [24, 31, 35, 37, 42–45]), ER/PR status (ER−/PR− [39, 43, 44, 48, 49, 51, 52] or ER+/PR+ [34, 39,

Table 2 Pooled measures on the relation of physical activity to breast cancer

	Random effect model	Fixed effect model	I^2 (%)	Number of studies	Number of breast cancer cases
Overall	0.87 (0.83–0.92)	0.88 (0.85–0.91)	29.5	31	63,786
Age-adjusted RR	0.85 (0.79–0.90)	0.88 (0.85–0.91)	54.3	18	29,321
RR with BMI unadjusted	0.90 (0.85–0.96)	0.89 (0.85–0.93)	35.5	14	34,664
RR with BMI adjusted	0.87 (0.83–0.91)	0.88 (0.85–0.91)	23.0	23	42,779
Follow-up years					
<10 years	0.87 (0.81–0.95)	0.89 (0.84–0.94)	29.3	12	16,853
>10 years	0.88 (0.83–0.93)	0.88 (0.84–0.91)	32.3	19	46,933
Location where the study was conducted					
America	0.88 (0.84–0.92)	0.89 (0.85–0.92)	20.9	20	29,994
Europe	0.87 (0.78–0.97)	0.87 (0.81–0.93)	35.7	8	32,216
Asia	0.82 (0.62–1.08)	0.88 (0.76–1.02)	65.3	3	1,576
Menopausal status					
Premenopausal	0.77 (0.69–0.86)	0.77 (0.72–0.84)	14.5	6	2,258
Postmenopausal	0.87 (0.87–0.92)	0.88 (0.84–0.92)	18.2	17	32,623
Body mass index (BMI)					
<25 kg/m^2	0.72 (0.65–0.81)	0.72 (0.65–0.81)	0.00	9	4,365
>25 kg/m^2	0.93 (0.83–1.05)	0.93 (0.83–1.05)	0.00	8	3,857
Estrogen receptor (ER) and progesterone receptor (PR) status (positive: +, negative: −)					
ER−/PR−	0.77 (0.65–0.90)	0.80 (0.73–0.87)	45.1	7	2,619
ER+/PR+	0.93 (0.87–0.98)	0.92 (0.87–0.98)	0.00	8	10,846
Tumor stage					
In situ	0.86 (0.74–0.99)	0.86 (0.74–0.99)	0.00	3	1,974
Invasive	0.81 (0.73–0.91)	0.84 (0.78–0.90)	38.5	5	8,100
Activity type					
Occupational	0.84 (0.73–0.96)	0.90 (0.83–0.97)	46.1	7	28,268
Non-occupational	0.87 (0.82–0.91)	0.87 (0.84–0.91)	27.7	27	37,568
Recreational	0.87 (0.83–0.91)	0.89 (0.85–0.92)	25.7	25	35,656
Household	0.89 (0.83–0.95)	0.89 (0.83–0.95)	0.00	3	11,932
Walking	0.87 (0.79–0.96)	0.88 (0.81–0.96)	7.90	5	5,708
Activity intensity					
Moderate	0.95 (0.90–0.99)	0.97 (0.94–0.99)	27.2	16	21,148
Vigorous	0.85 (0.80–0.90)	0.86 (0.82–0.89)	32.9	21	31,084
Periods of life during which physical activity was performed (years)					
<25	0.90 (0.81–1.02)	0.92 (0.84–1.00)	23.8	5	4,352
25–50	0.89 (0.83–0.95)	0.89 (0.84–0.93)	16.6	10	6,863
>50	0.83 (0.76–0.91)	0.88 (0.83–0.92)	42.2	11	17,966
Updated[a]	0.86 (0.80–0.92)	0.86 (0.80–0.92)	0.00	4	9,400

[a] Updated data of physical activity was used throughout the follow-up

43, 44, 48, 49, 51, 52]), and tumor stage (in situ [37, 43, 48] or invasive [27, 32, 37, 43, 48]). Stronger association of physical activity with breast cancer risk was found for premenopausal women (RR = 0.77, 95 % CI = 0.72–0.84, I^2 = 14.5 %), subjects with BMI <25 kg/m^2 (RR = 0.72, 95 % CI = 0.65–0.81, I^2 = 0.00 %), and ER−/PR− breast cancer (RR = 0.80, 95 % CI = 0.73–0.87, I^2 = 45.1 %).

Low or moderate between-study heterogeneity ($I^2 < 50$ %) was found in all analyses except for the analysis with studies conducted in Asia (I^2 = 65.3 %), and the result did not change materially using $I^2 > 50$ % as the criterion to reduce between-study heterogeneity after excluding one study [46] (RR = 0.92, 95 % CI = 0.79–1.08, I^2 = 31.8 %).

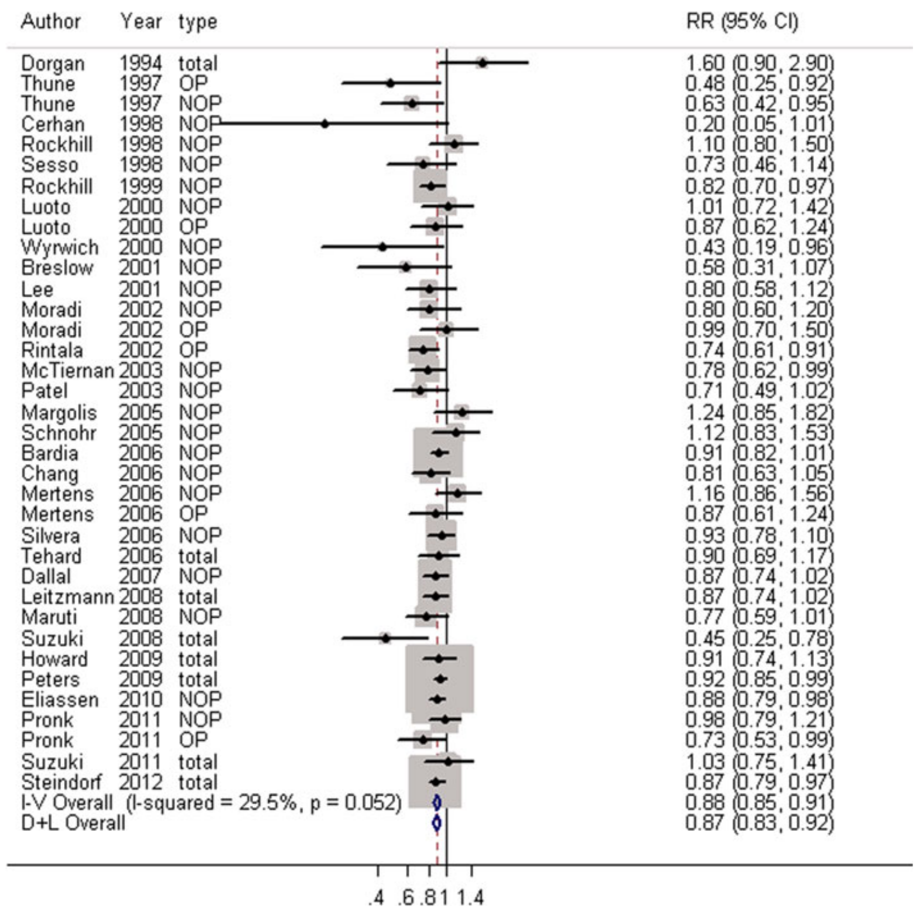

Fig. 2 The multivariate-adjusted risk of breast cancer for the highest versus lowest categories of physical activity. The size of *gray box* is positively proportional to the weight assigned to each study, which is inversely proportional to the standard error of the RR, and *horizontal lines* represent the 95 % confidence intervals. D + L denotes random effect model (REM), I–V denotes fixed effect model (FEM), NOP denotes non-occupational physical activity, and OP denotes occupational physical activity

Timing of physical activity

We assessed the importance of timing of activity by categorizing the periods of life during which physical activity was performed into four groups: <25 years [24, 28, 38, 45, 50], 25–50 years [24, 28, 33, 35–38, 45, 50, 51], >50 years [24, 26, 27, 32–34, 37, 39, 48, 49, 51], and throughout the follow-up [30, 43, 45, 49] (updated information of physical activity was used). Inverse association was found for activity done at <25 years (RR = 0.92, 95 % CI = 0.84–0.995, $I^2 = 23.8$ %), 25–50 years (RR = 0.89, 95 % CI = 0.84–0.93, $I^2 = 16.6$ %), >50 years (RR = 0.88, 95 % CI = 0.83–0.92, $I^2 = 42.2$ %), and throughout follow-up (RR = 0.86, 95 % CI = 0.80–0.92, $I^2 = 0.00$ %), respectively. Low or moderate between-study heterogeneity ($I^2 < 50$ %) was found in all analyses.

Dose–response analysis

Non-occupational activity

Data from three studies [42, 50, 52] including 12,175 breast cancer cases were used. Linear relationship was found between breast cancer risk and non-occupational activity (P for nonlinearity = 0.96), and the RR (95 % CI) was 0.98 (0.96–1.00), 0.95 (0.92–0.99), 0.93 (0.89–0.98), 0.91 (0.87–0.95), and 0.89 (0.84–0.94) for 25, 50, 75, 100, and 125 MET-h/week of non-occupational activity, respectively. The risk of breast cancer decreased by 2 %

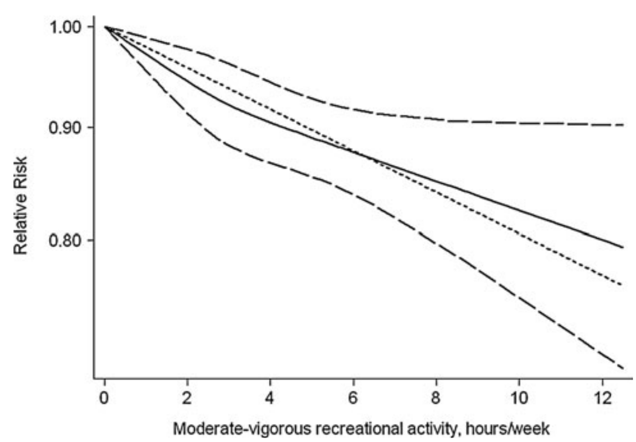

Fig. 3 The dose–response analysis between breast cancer risk and moderate plus vigorous recreational activity with restricted cubic splines in a multivariate random-effects dose–response model. The *solid line* and the *long dash line* represent the estimated relative risk and its 95 % confidence interval. *Short dash line* represents the linear relationship

(RR = 0.98, 95 % CI = 0.97–0.99, $P < 0.00$) for every 25 MET-h/week increment in non-occupational activity (roughly equivalent to 10 h/week of light household activity, such as cleaning dishes from table or cooking [11]).

Recreational activity

Data from seven studies [24, 37, 42, 45, 49, 50, 52] including 19,882 breast cancer cases were used. Linear relationship was found between breast cancer risk and recreational activity (*P* for nonlinearity = 0.45) and the RR (95 % CI) was 0.97 (0.95–0.99), 0.94 (0.91–0.98), 0.92 (0.89–0.96), 0.91 (0.87–0.94), 0.89 (0.85–0.94), and 0.88 (0.82–0.94) for 10, 20, 30, 40, 50, and 60 MET-h/week of recreational activity, respectively. The risk of breast cancer decreased by 3 % (RR = 0.97, 95 % CI = 0.95–0.98, $P < 0.00$) for every 10 MET-h/week increment in recreational activity (roughly equivalent to 4 h/week of walking in 2 miles/h [11]).

Moderate plus vigorous recreational activity

Data from eight studies [24, 28, 30, 41–43, 45, 47] including 13,877 breast cancer cases were used. Linear relationship was found between breast cancer risk and moderate plus vigorous recreational activity (*P* for nonlinearity = 0.36) and the RR (95 % CI) was 0.96 (0.93–0.99), 0.91 (0.87–0.95), 0.88 (0.85–0.92), 0.85 (0.80–0.91), and 0.83 (0.77–0.90) for 1.5, 3.5, 5.5, 7.5, and 9.5 h/week of moderate plus vigorous recreational activity, respectively. The risk of breast cancer decreased by 5 % (RR = 0.95, 95 % CI = 0.93–0.97, $P < 0.00$) for every 2 h/week increment in moderate plus vigorous recreational activity (Fig. 3).

Vigorous recreational activity

Data from eight studies [16, 24, 30, 41–43, 45, 47] including 11,958 cases were used. Linear relationship was found between breast cancer risk and vigorous recreational activity (*P* for nonlinearity = 0.18), and the RR (95 % CI) was 0.94 (0.91–0.98), 0.89 (0.85–0.94), 0.87 (0.82–0.92), 0.84 (0.78–0.91), and 0.82 (0.71–0.92) for 1.5, 3.5, 5.5, 7.5, and 9.5 h/week of vigorous recreational activity, respectively. The risk of breast cancer decreased by 5 % (RR = 0.95, 95 % CI = 0.92–0.97, $P < 0.00$) for every 2 h/week increment in vigorous recreational activity.

Sensitivity analysis and publication bias

Sensitivity analysis showed that no individual study had excessive influence on the pooled effect between risk of breast cancer and total physical activity, occupational activity, and non-occupational activity, respectively. Egger test showed no evidence of significant publication bias for the analysis between breast cancer risk and total physical activity ($P = 0.07$, Fig. 4), occupational activity ($P = 0.11$), and non-occupational activity ($P = 0.09$), respectively.

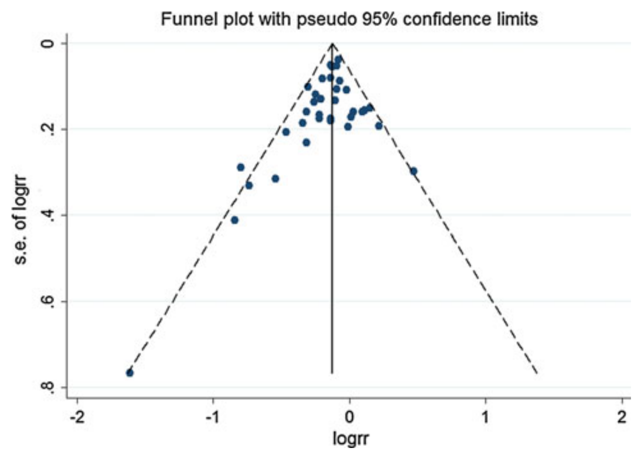

Fig. 4 Funnel plot for the analysis of breast cancer risk with physical activity overall

Discussion

Findings from this meta-analysis of prospective studies suggested that both occupational activity and non-occupational activity are significantly associated with reduced risk of breast cancer. Linear relationship was found between breast cancer risk and physical activity, and the breast cancer risk decreased by 2 % for every 25 MET-h/week increment in non-occupational activity, 3 % for every 10 MET-h/week increment in recreational activity, and 5 % for every 2 h/week increment in moderate plus vigorous recreational activity, respectively.

Physical activity might reduce the breast cancer risk through several biological mechanisms, including the impact of physical activity on adiposity, sex hormones, insulin resistance, adipokines, and inflammatory markers [53]. The pooled result from eight prospective studies of postmenopausal women showed that the RR for breast cancer incidence associated with a 5 kg/m^2 increment in BMI was 1.19 (95 % CI = 1.05–1.34) [54]. In the Cancer Prevention Study-II Nutrition Cohort, weight gain of 21–30 pounds was found associated with 40 % increment in breast cancer incidence (RR = 1.4, 95 % CI = 1.1–1.8), and the risk doubled among women gaining >70 pounds compared with women who maintained their weight within 5 pounds of their weight at age 18 [55]. And a randomized controlled trial suggested that a 1-year aerobic exercise intervention could reduce body weight, total body fat, intra-abdominal fat area, and subcutaneous abdominal fat area [56]. Thus, the observed protection might be partially attributed to reduced body weight or BMI. Sex hormones including estradiol, non-sex hormone-binding globulin (SHBG)-bound estradiol, estrone, estrone sulfate, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and testosterone had been shown to increase the risk of breast cancer [57], particularly for ER+/PR+ cancer [58]. And physical activity was also shown to influence sex hormone levels by reducing body fat and altering adipokine levels that could decrease hormone production [59] and lowering blood insulin levels, thereby increasing circulating SHBG levels that could reduce the bioavailability of sex hormones [60]. However, the stronger association between physical activity and ER−/PR− breast cancer, inconsistent with the hypothesis that physical activity acts through estrogen mediated by its receptor [61], suggested that physical activity does not exert its biological effects wholly through hormonal mechanisms [43]. Other possible mechanisms might involve the improved insulin sensitivity, decreased adipokine and oxidative stress levels and inflammatory markers, enhancing immune function, and suppressing procarcinogenic pathways and promoting anticarcinogenic pathways [53], and inducing a cancer-suppressing phenotype of tumor-associated macrophages [62].

Between-study heterogeneity is common in meta-analysis because of diversity in design quality, population stratification, characteristics of the sample, non-comparable measurement of physical activity, variation of the covariates, doses, and lengths of follow up, etc. [8]. And hierarchical systems for grading evidence state that the results of studies must be consistent or homogeneous to obtain the highest grading [63]. Low to moderate heterogeneity was found in most of the analysis, while moderate to high heterogeneity was found in two groups. Any reason that might account for the disease-effect unconformity will finally have an influence on the study-specific effect. Thus, we used the method proposed by Patsopoulos et al. [9] with $I^2 > 50\ \%$ as the criterion to assess the influence of between-study heterogeneity on the combined results by reducing between-study heterogeneity, and the results suggested that the association was robust in this meta-analysis.

A major strength of this study was the large number of participants included from prospective studies, allowing a much greater possibility of reaching reasonable conclusions and conducting subgroup analysis. And prospective studies do not suffer from recall bias and are anticipated to be less likely to have selection bias relative to case–control studies. However, there were some limitations in this meta-analysis. First, a wide range of definitions of physical activity have been used in previous studies as they have not uniformly assessed all types of physical activity (i.e., occupational, household, and recreational), the dose of activity (frequency, intensity, and duration), or all time periods in life when activity was performed [53]. Thus, misclassification as well as inaccurate measurement of physical activity might have led to some underestimation or exaggeration of the observed relation. Second, although we extracted the RRs that reflected the greatest degree of control for potential confounders, the possibility that the observed association was due to unmeasured or residual confounding should be considered. Besides, most studies included in this meta-analysis adjusted for BMI, which might induce over adjustment because the association between physical activity and breast cancer risk might be partially mediated via BMI. However, the result was similar in the multivariate-adjusted results without and then with adjustment for BMI. Finally, in a meta-analysis of published studies, it is possible that an observed association might suffer from publication bias because studies with null results tend not to be published. However, no significant publication bias was detected in this meta-analysis.

In summary, results from this meta-analysis indicated that physical activity is significantly associated with reduced risk of breast cancer. Physical activity should be advocated for the primary prevention of breast cancer.

Conflict of interest None.

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