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Systematic Literature Review

Physical Activity and Risk of Breast Cancer: A Meta-Analysis of 38 Cohort Studies in 45 Study Reports

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ABSTRACT

Objectives: To evaluate and quantify the association between physical activity (PA) and risk of breast cancer. **Methods:** A systematic review meta-analysis was conducted. The literature was independently and manually searched by 2 reviewers through 3 English databases (PubMed, Embase, and ISI Web of Science) for data till October 2017. The quality of included studies was assessed by the Newcastle-Ottawa Quality Assessment Scale. Fixed-effects models were used to estimate the pooled relative risk and 95% confidence intervals (95% CI). Dose–response analysis was chosen for quantifying the association between PA and risk of breast cancer. The Begg test and the Egger test were used to estimate potential publication bias. Heterogeneity between studies was evaluated with I^2 statistics. **Results:** The meta-analysis included 38 cohort studies published between 1994 and 2017, which included 68 416 breast cancer cases. The overall relative risk (ORR) for breast cancer was 0.87 (95% CI 0.84-0.90). The inverse association was consistent among all subgroup analyses. In subgroup analysis by menopausal status, the ORR of breast cancer was 0.83 (95% CI 0.79-0.87) for premenopausal status and 0.91 (95% CI 0.85-0.97) for postmenopausal status. In subgroup analysis by PA type, the ORR for total activity was 0.87 (95% CI 0.81-0.93), for recreational activity 0.88 (95% CI 0.85-0.91), for occupational activity 0.91 (95% CI 0.84-0.99), and for nonoccupational activity 0.87 (95% CI 0.83-0.92). The risk of breast cancer was significantly lower in people with exposure periods longer than 1 year and less than 5 years (ORR 0.62; 95% CI 0.46-0.78), followed by those with lifetime activity (ORR 0.81; 95% CI 0.69-0.93). The ORR for subjects with body mass index of less than 25 kg/m^2 (0.88; 95% CI 0.83-0.93) was close to that for subjects with body mass index of more than 25 kg/m^2 (0.87; 95% CI 0.77-0.97). A linear relationship was found between breast cancer risk and PA (recreational activity and total activity), and the ORR was reduced by 3% (95% CI 0.95-0.99) for every 10 metabolic equivalent of energy hours per week increment in recreational PA and by 2% (95% CI 0.97-0.99) for every 10 metabolic equivalent of energy hours per week increment in total PA. **Conclusions:** PA is significantly associated with a decrease in the risk of breast cancer.

Keywords: breast cancer, meta-analysis, physical activity, systematic review

Introduction

From 1970 to 2016, life expectancy at birth overall increased by 13.5 years for men and 14.8 years for women.[1] Nevertheless, the incidence of cancer has led to a decrease in the expected increase in life expectancy. Deaths from neoplasms increased globally by 17.8%, rising from 7.58 million deaths in 2006 to 8.93 million deaths in 2016. Breast cancer deaths increased from 466,000 in 2006 to 546,000 in 2016.[2] In 1985, Frisch et al[3] found a 44% reduced rate of breast cancer among female college athletes through a small study on 69 breast cancer cases. Since then, epidemiological studies have generally corroborated the inverse association between physical activity (PA) and breast cancer.[4,5] A minimum of 150 min/wk of moderate to vigorous PA is recommended generally for cancer prevention.[6] In 1998, Dorgan et al[7] stressed that a decrease in risk of breast cancer with increasing levels of PA is intuitively appealing, but there was at that time a disappointing lack of consistency in the findings of epidemiological studies.

Because of potentially different biological mechanisms relating PA to premenopausal and postmenopausal breast cancer risk, respectively, menopausal status warrants careful consideration.[8] The mechanisms are still not clear, especially for premenopausal breast cancer. Two systematic reviews[9,10] concluded that increment in PA levels reduces the risk of postmenopausal breast cancer probably, whereas the evidence for premenopausal breast cancer risk was "limited."

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PA is often negatively correlated with body mass index (BMI); people often do exercise regularly for controlling weight. Renehan et al[11] found a 25% increased risk for a gain of 10 kg/m^2 (approximately equivalent to the contrast between normal-weight women and obese women), which is a higher estimate than the 14% found in this study. The role of BMI is also important in confounding variables. The result of BMI adjustments should be interpreted cautiously, because BMI may be the causal pathway between PA and breast cancer risk. If this is the case, then adding BMI as a confounding factor will diminish the impact of PA.[12]

In this study, our main aim was (1) to explore the heterogeneity among studies and publication bias; (2) to quantify the association between PA and breast cancer risk in prospective studies; (3) to explore in more depth the influence that exposure assessment and breast cancer risk factors have, especially BMI; and (4) to evaluate the possible dose–response relationship between PA and breast cancer risk.

Methods

Search and Selection of Literature

We performed a literature search in PubMed, Embase, and ISI Web of Science databases for data till October 2017. A combination of keywords and Medical Subject Headings index terms was used including "breast cancer" or "breast neoplasm"; "physical activity," "physical exercise," or "motor activity"; and "cohort." For example, we searched in PubMed using the following format: ((((((breast cancer [Title/Abstract]) OR breast neoplasm [Title/Abstract]) AND physical activity [Title/Abstract]) OR physical exercise [Title/Abstract]) OR motor activity [Title/Abstract]) AND cohort [Title/Abstract]). There were no restrictions by language, date, or geographical location. Moreover, the reference lists of relevant review articles were searched manually to identify additional studies.

Title and abstracts were screened for eligibility. Full copies of eligible articles were retrieved and fully read by 2 of the investigators, and studies were included if they met the following criteria[12]: (1) the study had a prospective design; (2) the exposure of the study was PA; (3) the outcome of interest was breast cancer; (4) the study reported measurement of PA; (5) multivariate-adjusted relative risk (RR) or hazard ratio (HR), with 95% confidence interval (CI), was provided; and (6) for dose–response analyses, the number of cases and participants or person-years for each category of PA were provided (or data available to calculate them). To track the latest research, when several articles were based on the same study, the most recent publication was selected.

Data Extraction

The data extraction and study quality assessment were independently performed by 2 reviewers. Any disagreement was discussed and resolved by the third reviewer. Data were extracted using standardized data extraction forms specifically created for this review and were subsequently entered into a database. All data entry was double-checked. The following data were extracted from each study: the first author's last name, publication year, location where the study was performed (North America, Europe, or Asia), cohort's name, age of study group, follow-up duration, sample size and number of cases, PA type (total, recreational, occupational, or nonoccupational), menopausal status (premenopausal or postmenopausal), RR or HR estimates with corresponding 95% CI, PA measure and the period of life during which PA was performed ($t \leq 1$ year, $1 < t < 5$ years, $t \geq 5$ years, or lifetime), BMI before PA exposure assessment, and variables adjusted for in the analysis. We extracted the RRs that reflected the greatest degree of control for potential confounders.

We established decision rules for data extraction that aligned with our primary aim. If multiple RR estimates were reported for different life periods, the estimate associated with the longest and most recent PA was extracted. If RR estimates were provided separately for in situ and invasive breast cancer risk, we extracted results for invasive cancer. To be able to evaluate whether the risk of breast cancer is modified by menopausal status or BMI, we extracted the relevant data of all articles addressing these issues. If available, we also extracted the age-adjusted RRs and multivariate-adjusted RRs without adjustment for BMI.

For dose–response analyses, the number of cases and participants or person-years for each category of PA must also be provided (or data available to calculate them). If multiple RR estimates were reported for different units of activity, we extracted data only in metabolic equivalent of energy (MET) hours per week (MET-h/wk).

Quality Assessment

Our approach to assessing study quality was influenced by a review 10 years ago[13] and by the Newcastle-Ottawa Quality Assessment Scale (NOS) for included cohort studies.[14] The NOS items were based on 3 dimensions: selection of study groups, comparability of the groups, and ascertainment of either the exposure or outcome of interest. We classified quality on the basis of 3 levels (total score was 9): high quality, with scores between 8 and 9; moderate quality, with scores between 5 and 7; and low quality, with scores between 0 and 4. Study quality assessment was performed by 2 reviewers independently. We labeled all selected studies as given in Table 1, and we extracted articles with only high quality (A) or moderate quality (B).

Statistical Methods

For primary analyses, pooled RRs and 95% CIs were calculated using the random-effects model. Statistical heterogeneity among studies was evaluated using the Q and I^2 statistics.[15] For Q test, consistent with chi-square distribution, a 2-tailed P value of less than .100 was considered heterogeneous. In addition, we used I^2 values to determine heterogeneity between different studies. The I^2 values represent the percentage of true heterogeneity (unsampled error) in total variance.[15] The method proposed by Patsopoulos et al[16] was used, with an I^2 of more than 50% as the criterion to assess the influence of between-study heterogeneity. If heterogeneity exists, the random-effects model ($I^2 > 50\%$) is used; otherwise, the fixed-effects model ($I^2 < 50\%$) is adopted.[17] Subgroup analysis included the location where the study was conducted, the period of life (t) during which PA was performed, menopausal status at onset, PA type, quantification of PA, and BMI adjusted or nonadjusted.

The Egger test and the Begg test were used to assess publication bias[18,19] and represented by funnel plot. If publication bias existed, we analyzed its impact on the result.

Quantitative reviews of published epidemiological studies of exposure–response relations typically include an assessment of the relation between exposure levels and risk of disease.[20] So we performed a random-effects dose–response analysis using RR estimates based on activity volume (MET-h/wk). We did not convert hours per week (h/wk) to MET-h/wk or vice versa. If the upper and lower limits of the section were provided in a group, the dose was equal to 1/2 times the sum of the upper limit and the lower limit. If the upper boundary of the highest category or the lower boundary of the lowest category was not provided, the

Table 1 – Characteristics of prospective studies on PA and breast cancer

Study	Country	Study name	Age (y)	Follow-up (y)	Sample size	Case
Dorgan et al[7]	United States	The Framingham Heart Study	35-68	28	2,298	117
Thune et al[65]	Norway	The national health screening service	20-54	13.7	25,624	351
Fraser and Shavlik[66]	United States	The Adventist Health Study	>24	6	20,341	218
Cerhan et al[63]	United States	The Iowa 65+ Rural Health Study	62-102	21	1,806	46
Sesso et al[64]	United States	The College Alumni Health Study	37-69	32	1,566	109
Luoto et al[60]	Finland	The Finnish Adults Health Behavior Survey	15-64	16	30,548	332
Wyrwich and Wolinsky[61]	United States	The Longitudinal Study on Aging	70-98	8	3,131	77
Wyshak and Frisch[62]	United States	The College Alumnae	21-80	15	5,398	175
Breslow et al[57]	United States	NHANES I	24-75	9.2	6,160	138
Lee et al[58]	United States and Puerto Rico	The Women's Health Study	>45	4	39,322	411

Table 1 – *continued*

Menopausal status	PA type	Activity measure and life period	Average BMI*	Contrast and RR estimate (95% CI)	Adjustment for covariates	NOS grade
Post	Total	Summary score; recent[†]	Cases: 24.9 Noncases: 25.1	33-54 summary score vs 25-28 summary score; HR = 1.60 (0.90-2.90), *P* for trend = .060	Age, number of pregnancies, menopausal status, age at first pregnancy, education, occupation, and alcohol ingestion	B
Post/pre	Recre	Subjective; recent (3-5 y)	24.9[§]	Regular exercise vs sedentary; RR = 0.63 (0.42-0.95), *P* for trend = .040; heavy vs sedentary; RR = 0.48 (0.25-0.92), *P* for trend = .020	Age at entry, BMI, height, county of residence, and number of children	B
Post/pre	Occ and noc	Min/wk; recent	24.3	High vs low; HR = 0.68 (0.52-0.90); *P* for trend = unknown	Education, parental history of cancer, HRT use, age at first delivery, BMI, and physical inactivity	B
Post	Noc	Summary score; recent	24.7	High vs inactive; RR = 0.20 (0.05-1.00), *P* for trend = .006	History of breast cancer, personal history of benign breast disease, and employed (yes/no)	B
Post/pre	Noc	Caloric expenditure; recent	22.4[§]	>1000 vs <500 cal/wk; RR = 0.73 (0.46-1.14), *P* for trend = .170	Age, BMI	B
Post/pre	Recre and occ	Frequency; recent Min/d; recent	23.5[§]	Recre: daily vs less than once a week; RR = 1.01 (0.72-1.42), *P* for trend = .500; Occ: >30 min/d vs unemployed work at home; RR = 0.87 (0.62-1.24), *P* for trend = .830	Education, parity, age at first birth, number of children, and BMI	B
Post	Noc	Subjective; recent	–[‡]	high vs inactive; HR = 0.42 (0.19-0.95), *P* for trend = unknown	Previous cancer, age, BMI, education, and previous doctor visits	B
Post/pre	Noc	Athletes/nonathletes; college time	Athletes: 23.3 Nonathletes: 23.3	Athletes vs nonathletes; OR = 0.61 (0.44-0.84), *P* for trend = .0023	Age in single years, ever-pregnant, OC use, HRT use, family history of breast cancer, current exercise, ever smoked, percent body fat	B
Post/pre	Recre	Subjective; recent	25.1	Consistently high vs consistently low; RR = 0.58 (0.31-1.07), *P* for trend = .107	Height, BMI at age 25 y, adult weight change (age 25 y to age at 1982-1984 interview), and sample design variables	B
Post/pre	Noc	Caloric expenditure kJ/wk; recent	Cases: 25.1 Noncases: 25.8	≥6300 vs <840 kJ/wk; RR = 0.80 (0.58-1.12), *P* for trend = .110	BMI, alcohol consumption, age at menarche, age at first pregnancy lasting ≥6 mo, number of pregnancies lasting ≥6 mo, menopausal	B

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Table 1 – *continued*

Study	Country	Study name	Age (y)	Follow-up (y)	Sample size	Case
Dirx et al[59]	The Netherlands	The Netherlands Cohort Study	55-69	7.3	62,537	1,208
Moradi et al[56]	Sweden	The Swedish Twin Registry	42-70	27-30	9,593	506
Rintala et al[52]	Finland	The Finnish Female Physical Education Study and Language Teachers Study Cohort	>25	34	10,049	465
Schnohr et al[50]	Denmark	The Copenhagen Centre for Prospective Population Studies	20-93	14	13,216	417
Margolis et al[51]	Norway and Sweden	The Women's Lifestyle and Health Study Cohort	30-49	9.1	99,504	1,166
Bardia et al[45]	United States	The Iowa Women's Health Study	55-69	18	41,836	2,548
Chang et al[46]	United States	The PLCO Cancer Screening Trial	55-74	11	38,660	764

Table 1 – *continued*

Menopausal status	PA type	Activity measure and life period	Average BMI*	Contrast and RR estimate (95% CI)	Adjustment for covariates	NOS grade
					status, OC use, MHT use, family history of breast cancer	
Post	Recre	min/d; lifetime	–[‡]	>90 vs <30 min/d; RR = 0.76 (0.58-0.99), *P* for trend = .003	Age, age at menarche, age at menopause, benign breast disease, parity, age at first birth, maternal breast carcinoma, breast carcinoma in sister(s), education, height, and baseline alcohol and energy intake	B
Post/pre	Recre and occ	Subjective; recent	24.5[§]	Recre: regular activity vs sedentary; RR = 0.8 (0.6-1.2), *P* for trend = .300 Occ: strenuous vs sedentary RR = 1.0 (0.7-1.5), *P* for trend = .900	Age	B
Post/pre	Occ	Different teacher; lifetime	–[‡]	Physical education teachers vs language teachers; RR = 0.83 (0.63-1.09), *P* for trend = unknown	Age, calendar time and age at first birth, and the number of children	B
Post	Noc	Three levels of PA; past year	–[‡]	Vigorous vs low; RR = 1.12 (0.83-1.53), *P* for trend = .450	Age, birth cohort, study cohort Membership, occupational PA, smoking, education, alcohol consumption, BMI, parity	B
Pre	Recre	Subjective; recent	23.2	Vigorous activity vs no activity; RR = 1.24 (0.85-1.82), *P* for trend = .850	Age at enrollment, 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, country of origin	B
Post	Noc	Frequency times/wk; recent	26.8[§]	High vs low; RR = 0.91 (0.82-1.01), *P* for trend = .130	Age, education 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 use, smoking, BMI	B
Post	Recre	h/wk; recent	27.0[§]	≥4 vs 0 h/wk; RR = 0.81 (0.63-1.05), *P* for trend = .302	Study center, race, height, family history of breast cancer, history of benign breast disease, age at menarche, age at first birth, parity,	B

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Table 1 – *continued*

Study	Country	Study name	Age (y)	Follow-up (y)	Sample size	Case
Mertens et al[47]	United States	The ARIC Study	45-64	13.1	7,994	342
Silvera et al[48]	Canada	NBSS	40-59	16.4	40,318	1,673
Leitzmann et al[42],‖	United States	The BCDDP Study	>60	12	32,269	1,506
Suzuki et al[43]	Japan	The Japan Collaborative Cohort Study	40-69	12.4	30,157	207
Howard et al[40]	United States	The USRT Cohort	46.5 (mean)	8.9	45,631	864

Table 1 – *continued*

Menopausal status	PA type	Activity measure and life period	Average BMI*	Contrast and RR estimate (95% CI)	Adjustment for covariates	NOS grade
					education, age at menopause, MHT use, energy intake, BMI	
Post/pre	Occ and noc	PA index; recent	63.0% with BMI ≥25[§]	Q4 vs Q1 Noc: HR = 1.00 (0.64-1.54), *P* for trend = .830 Occ: HR = 0.87 (0.61-1.24), *P* for trend = .180	Age, race, and center age at first live birth, age at menopause, family history of breast cancer in 1 first-degree relative	B
Post/pre	Recre	min/d; recent	38.9% with BMI ≥25[§]	>60 vs 0-30 min/d; HR = 0.93 (0.78-1.10), *P* for trend = .380	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 at baseline, menopausal status, study center and randomization group, energy intake, BMI	B
Post	Total	MET-h/wk; recent	41.8% with BMI ≥25[§]	395-721 vs 105-244 MET-h/wk RR = 0.87 (0.74-1.02), *P* for trend = .210	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, history of OC use, HRT use, education attainment, smoking, intakes of energy-adjusted dietary fat and alcohol, BMI	B
Post/pre	Recre	h/d in walking and h/wk in exercising; recent	22.8[§]	≥1 h/d spent on Walking and ≥1 h/wk spent on exercising vs<1 h/d spent on walking and <1 h/wk spent on exercising; HR = 0.45 (0.25-0.78), *P* for trend = .041	Age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, meno pausal status, and menopausal age for postmenopausal women	A
Post/pre	Total	MET-score; past year	25.4[§]	≥97.0 vs <9.5 MET-score; RR = 0.91 (0.74-1.13), *P* for trend = .174	Age, BMI, parity, age at menarche, age at first birth, age at menopause, family history of breast disease, OC use, HRT use, race, smoking, alcohol	B

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Table 1 – *continued*

Study	Country	Study name	Age (y)	Follow-up (y)	Sample size	Case
Pronk et al[37]	China	SWHS	40-70	9	73,049	717
Suzuki et al[36]	Japan	The JPHC-Based Prospective Study	40-69	14.5	53,578	652
Phipps et al[38,¶]	United States	WHIOS	50-79	7.9	155,723	2,917
Mctiernan et al[53,‖,#]	United States	WHIOS	50-79	4.7	74,171	1,780
Steindorf et al[35,¶]	Europe	The multinational EPIC Cohort Study	20-98.5	11.6	257,805	8,034
Hastert et al[33]	United States	The Vitamins and Lifestyle (VITAL) Study Cohort	50-76	6.7	30,797	899

Table 1 – *continued*

Menopausal status	PA type	Activity measure and life period	Average BMI*	Contrast and RR estimate (95% CI)	Adjustment for covariates	NOS grade
Post	Noc	MET-h/wk (y); past years	Cases: 24.0 Cohort: 24.2	>131.5 vs <74.3 h/wk HR = 0.98 (0.79-1.21), *P* for trend = .640	Age, education, family history of breast cancer, age at first birth, and number of pregnancies	B
Post/pre	Recre	d/wk, d/mo, METs/d score; recent	23.3[§]	Recre: ≥3 d/wk vs ≤3 days/mo; RR = 0.73 (0.54-1.00), *P* for trend = .060 Total: tertile3 vs tertile1; RR = 1.03 (0.75-1.41), *P* for trend = .860	Age, area, height, recent BMI, BMI at age 20 y, smoking status, age at menarche, age at first birth, parity, age at menopause, use of exogenous female hormones, alcohol intake, energy-adjusted intake of isoflavones	A
Post	Recre	MET-h/wk; baseline	Cases: 32.4% with BMI ≥28.4[§]	≥16.5 vs <0.01 MET-h/wk; ER+:HR = 0.85 (0.74-0.98), *P*<.010	Age, education, income, family history of breast cancer, race, history of mammography, mammography during follow-up, BMI at baseline	B
Post	Recre	MET-h/wk; recent	Cases: 32.4% with BMI ≥28.4[§] Noncases: 32.3% with BMI ≥28.4[§]	>40 vs 0 MET-h/wk RR = 0.78 (0.62-1.00), *P* for trend = .300	Age, BMI, hormone therapy status, race, geographic region, income, education, ever breast-fed, hysterectomy status, first-degree relative with breast cancer, smoking status, parity, age at first birth, number of mammograms in 5 y before study enrollment, alcohol use as categorical variables, age at menarche, age at menopause	B
Post/pre	Total	MET-h/wk; past year	24.9[§]	Recre: >42 vs <13.5 MET-h/wk; HR = 0.96 (0.90-1.03), *P* for trend = .224 Occ: Heavy manual vs sedentary; HR = 0.96 (0.88-1.06), *P* for trend = unknown Total: active vs inactive; HR = 0.87 (0.79-0.97), *P* for trend = .002	BMI, age at first period, age at first full-term pregnancy, number of full-term pregnancies, breast-feeding, ever OC pill, menopausal status, age at menopause, use of hormone replacement therapy, alcohol consumption, smoking status, level of school attained; mutually adjusted for other types of PA	B
Post	Recre	min/d, d/wk; the previous 10 y	—[‡]	Meeting guidelines vs not meeting guidelines; HR = 0.97	Age, education, race, mammography, family history of breast cancer, age at	A

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Table 1 – *continued*

Study	Country	Study name	Age (y)	Follow-up (y)	Sample size	Case
Hildebrand et al[34,¶]	United States	The CPS-II Nutrition Cohort	50-74	14 (median)	73,615	4,760
Patel et al[54,#]	United States	The CPS-II Nutrition Cohort	50-74	5	72,608	1,520
Brinton et al[30]	United States	The NIH-AARP Diet and Health Study	50-71	7	190,872	7,384
Peters et al[41,#]	United States	The NIH-AARP Diet and Health Study	50-71	7	182,862	6,609
Fournier et al[31]	France	The E3N Cohort	40-65	8.5	59,308	2,155

Table 1 – *continued*

Menopausal status	PA type	Activity measure and life period	Average BMI*	Contrast and RR estimate (95% CI)	Adjustment for covariates	NOS grade
				(0.81-1.16), *P* for trend = unknown	menarche, age at first birth, age at menopause, years of ER and PR, HRT use, whether respondents met other recommendations	
Post	Recre	MET-h/wk; baseline	62.8% with BMI ≥25§	>42 vs 0 MET-h/wk; RR = 0.75 (0.63-0.89), *P* for trend = .050	Age, race, education, BMI, weight change, alcohol use, smoking status, PMH use, number of live births, age at first live birth, age at menopause, family history of breast cancer, oophorectomy, hysterectomy, breast cysts, mammogram within last year	A
Post	Recre	MET-h/wk; recent	46.5% with BMI ≥25§	>42.0 vs 0-0.7 MET-h/wk; RR = 0.71 (0.49-1.02), *P* for trend = .080	Age, race, BMI, weight change from age 18 to 30 y, family history of breast cancer, personal history of breast cysts, duration of OC use, HRT use, parity, age at menarche, age at menopause, smoking, alcohol intake, caloric intake, education, mammography history	A
Post	Recre	Frequency times/wk or mo; past year	26.9	≥5 times/wk vs <1 time/month; HR = 0.91 (0.85-0.99), *P* for trend = .020	Race, education level, marital status, age at menopause, parity, age at first live birth, age and type of menopause, MHT use, BMI, daily intake, family history of breast cancer in a first-degree relative, number of previous breast biopsies	B
Post	Total	Frequency; recent	26.9	≥5 vs <1 time/wk; RR = 0.92 (0.85-1.00), *P* for trend = .040	Age, race, education level, smoking, family history of breast cancer, HRT use, parity, age at first birth, age at menarche, age at menopause, alcohol, BMI	B
Post/pre	Recre	MET-h/wk; previous 4 y	24.9§	≥36 vs <12 MET-h/wk; HR = 0.93 (0.83-1.05), *P* for trend = .690	Age, family history of breast cancer in first-degree relatives, age at menarche, parity and age at first full-term pregnancy, BMI,	B

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Table 1 – *continued*

Study	Country	Study name	Age (y)	Follow-up (y)	Sample size	Case
Tehard et al[49,‖,¶,#]	France	The E3N Cohort	40-65	13	90,509	3,424
Borch et al[32]	Norway	The NOWAC Study	34-70	8.2 (median)	80,202	1,767
Zhang et al[29]	United States	NHS	30-55/40-65	26	103,577	2,118
Eliassen et al[39,‖,#]	United States	NHS	40-65	20	95,396	4,782
McKenzie et al[28]	European countries	The EPIC and Nutrition Cohort	25-70	10.9 (median)	242,918	7,756
Hallmarker et al[27]	Sweden	The Vasaloppet Ski-race Study	>20	9.8 (median)	370,029	1,704

Table 1 – *continued*

Menopausal status	PA type	Activity measure and life period	Average BMI*	Contrast and RR estimate (95% CI)	Adjustment for covariates	NOS grade
					history of benign breast disease, age at menopause, HRT use, total energy intake excluding alcohol, alcohol intake, further stratified by year of birth	
Post/pre	Total/recre	MET-h/wk; recent	—‡	Total: ≥57.8 vs<28.3 MET-h/wk; RR = 0.90 (0.80-1.02), *P*<.050 Recre: >33.8 vs <16 MET-h/wk; RR = 0.81 (0.72-0.92), *P* for trend <.010	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 cancer, personal history of benign breast disease, and employed (yes/no)	B
Post	Occ and noc	5 levels of PA	26.1% with BMI ≥25§	Level 5 vs level 3; RR = 0.91 (0.73-1.12), *P* for trend = .400	Height, BMI, smoking status, smoking duration, age at menarche, OC use, age at first birth, parity, HRT use, self-reported disease, history of breast cancer in the participant's mother	B
Post	Recre	MET-h/wk; past year	—‡	≥27 vs <3 MET-h/wk; RR = 0.86 (0.78-0.95), *P*<.001	Age at menarche, BMI at age 18 y, height, parity, age at first birth, alcohol intake, PMH use, age at menopause, family history of breast cancer, history of benign breast disease	B
Post	Noc	MET-h/wk; past year	26.5§	≥27 vs <3 MET-h/wk; HR = 0.88 (0.79-0.98), *P* for trend = .003	Age at menarche, BMI at age 18 y, height, parity, age at first birth, alcohol intake, PMH use, age at menopause, family history of breast cancer, history of benign breast disease	B
Post	Noc	METs/wk; baseline	25	>134 vs <45 METs/wk; HR = 0.87 (0.80-0.95), *P* for trend = .001	Study center and age, height, age at menarche, age at first pregnancy, education, HRT use, OC use, breast-feeding, nonalcohol energy intake, other index components	B
Post/pre	Noc	Ski or nonparticipants; past year	—‡	Skiers vs nonparticipants Pre: RR = 1.02 (0.88-1.19),	Age, sex, county of residence	B

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Table 1 – *continued*

Study	Country	Study name	Age (y)	Follow-up (y)	Sample size	Case
Nomura et al[25]	United States	The Black Women's Health Study (BWHS)	21-69	13.86 (average)	49,103	1,827
Liu et al[26,‖]	United States	The Nurses' Health Study II(NHS-II)	22-44	23	65,576	2,069
Colditz et al[55,#]	United States	The Nurses' Health Study II(NHS-II)	25-42	10	110,468	849
Ma et al[24]	United States	The California Teachers Study	22-79	10	108,907	5,882
Dallal et al[44,#]	United States	The California Teachers Study	20-79	6.6	110,599	2,649

Table 1 – *continued*

Menopausal status	PA type	Activity measure and life period	Average BMI*	Contrast and RR estimate (95% CI)	Adjustment for covariates	NOS grade
				P for trend = .774 Post: RR = 0.97 (0.86-1.11), *P* for trend = .688		
Post/pre	Recre	WCRF/AICR guideline adherence scores; recent	61.5% with BMI ≥25[§]	Adherence vs no adherence; HR = 0.85 (0.74-0.97), *P* for trend = .030	Age, geographic region of residence, kilo calories/d, smoking, family history of breast cancer, education, menopausal status, OC use, parity, menopausal hormone use, BMI, alcohol	A
Post/pre	Total	MET-h/wk; past year	23.9[§]	≥58 vs <24 MET-h/wk; RR = 0.91 (0.79-1.05), *P* for trend = .240	Age, questionnaire year, alcohol intake, average childhood body size, history of benign breast biopsy, family history of breast cancer, height, total duration of breast-feeding, duration and frequency of OC use, menopausal status, PMH use, birth index, PA after first pregnancy	B
Pre	Total	MET-h/wk; recent	26.0[§]	>27 vs <3 MET-h/wk; RR = 1.04 (0.82-1.33); *P* for trend = .860	Age, height, BMI, alcohol intake, age at menarche, age at first birth, OC use, history of benign breast disease, mother or sister with breast cancer	B
Pre	Recre	h/wk/y	41.1% with BMI ≥25[§]	≥7.01 vs ≤0.50 h/wk/y; HR = 0.90 (0.81-0.99), *P* for trend = .010	Race, family history of breast cancer in first-degree relatives, combined age at first full-term pregnancy and parity variable, combined menopausal status and MHT use variable, BMI at baseline, history of smoking, alcohol intake during the past year of baseline, screening mammogram in the past 2 y of baseline, history of a breast biopsy	B
Post/pre	Recre	h/wk; lifetime	24.9	>5 vs <0.5 h/wk Moderate: RR = 0.94 (0.81-1.08), *P* for trend = .290	Race, family history of breast cancer, age at first full-term pregnancy, hormone	B

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Table 1 – *continued*

Study	Country	Study name	Age (y)	Follow-up (y)	Sample size	Case
Niehoff et al[23]	United States and Puerto Rico	The Sister Study	35-74	6.4	50,884	2,416

Note. NOS scores: grade A, 8-9; grade B, 5-7; grade C, ≤4.
ARIC indicates Atherosclerosis Risk in Communities; BCDDP, Breast Cancer Detection Demonstration Project Follow-Up; BMI, body mass index; BWHS, Black Women's Health Study; CI, confidence interval; CPS, Cancer Prevention Study; EPIC, European Prospective Investigation into Cancer; HR, hazard ratio; HRT, hormone replacement therapy; JPHC, Japan Public Health Center; MET, metabolic equivalent of energy; MHT, menopausal hormone therapy; NBSS, National Breast Screening Study; NHANES I, National Health and Nutrition Examination Survey I; NHS, Nurses' Health Study; NIH-AARP, National Institutes of Health (formally the American Association of Retired Persons); Noc, nonoccupational; NOS, Newcastle-Ottawa Scale; NOWAC, Norwegian Women and Cancer; OC, contraceptive; Occ, occupational; PA, physical activity; PLCO, Prostate, Lung, Colorectal, and Ovarian; Post, postmenopausal; Pre, premenopausal; Recre, recreational; RR, relative risk; SWHS, Shanghai Women's Health Study; USRT, US Radiologic Technologists; VITAL, Vitamins and Lifestyle; WHIOS, Women's Health Initiative Observational Study.
* If the mean or median BMI was not reported (or could not be calculated using the data provided in the article), then the proportion of women in the highest BMI category is shown.
† Recent refers to activity within the past 1-8 y or time not specified (and therefore assumed recent).
‡ Data not reported.
§ Approximated from data reported in article.
‖ These studies were also used for the dose–response analysis on total activity.
¶ These studies were also used for the dose–response analysis on recreational activity.
# Studies that are not included in the primary analysis but are included in subgroup analyses.

dose was equal to the end value plus or minus 1/2 times the product of the distance between adjacent groups. To model activity in relation to breast cancer risk, we used restricted cubic splines with 4 knots at fixed percentiles in the distribution of recreational PA and total PA. The Wald test was used to assess nonlinearity (testing the null hypothesis that the regression coefficients of the second spline and the third spline were equal to 0 for the same time[21,22]; if P <.050, a nonlinear dose–response was considered; otherwise, a linear dose–response was considered).

All statistical analyses were performed using Stata version 12.0 (Stata Corp, College Station, Texas), and we considered P values of less than .050 (2-sided) to be statistically significant.

Results

Literature Search

We identified 1532 records in our database search; 12 of them came from reference lists. After Removing duplicates and excluding on title and abstract (title/abstract screening was done by 2 independent reviewers) resulted in 96.5% (996 of 1032) agreement on inclusion/exclusion ($\kappa = 0.922$). The records of 115 articles were eligible for full-text screening. After full-text review and verification, 58 records qualified for inclusion. After removing duplicate studies, there were finally 45 articles (Fig. 1) (7 studies for subgroup analysis).

Quality Assessment

The NOS grades for all the 45 studies are presented in Table 1, and they were considered to be "good quality" (NOS scores were >4).

Study Characteristics

Study characteristics for the 45 articles[7,23–50,51–66] are also presented in Table 1. All of them are from cohort studies. There were 24 cohort studies[7,23–26,29,30,33,34,38,40,42,45–48,57–59,61–64,66] from North America, 11 cohort studies[27,28,31,32,35,50–52,56,60,65] from Europe, and 3 cohort studies[36,37,43] from Asia. Thirty-eight studies[7,23–40,42,43,45–48,50–52,56–62,64–66] were included in our primary results. An additional 7 reports[28,39,41,44,49,54,55] described the same study populations as in the primary analysis, but we extracted only their subgroup results. Seven studies[7,26,35,36,40,42,66] reported total

Table 1 – *continued*

Menopausal status	PA type	Activity measure and life period	Average BMI*	Contrast and RR estimate (95% CI)	Adjustment for covariates	NOS grade
				Strenuous: RR = 0.80 (0.69-0.94), *P* for trend = .020	therapy, menopausal status combined variable, BMI, smoking history, alcohol consumption, history of breast biopsy, mammography screening	
Post/pre	Recre	h/wk; past year	—‡	>7 vs 0-1 h/wk; HR = 0.75 (0.57-0.99), *P* for trend = unknown	Race, urban/rural childhood residence, family income while growing up, highest education in household growing up, age at fruit and vegetable intake (frequency of servings)	B

PA, 21 studies[23–25,29–36,38,43,46,48,51,56,57,59,60,65] reported recreational PA, 6 studies[35,47,52,56,60,65] reported occupational PA, and 11 studies[27,28,37,45,47,50,58,61–64] reported nonoccupational PA. Twenty-six studies[7,24–26,28,29,34–36,42,43,45–48,50,52,56,57,60–66] had a short follow-up time of more than 10 years, and the duration of follow-up in 12 studies[23,27,30–33,37,38,40,51,58,59] was less than 10 years. As for the period of life for which PA was performed, 14 studies[25,26,29–31,34,35,39–41,50,54,58,66] reported PA for no more than 1 year, 2 studies[49,62] for 1 to 5 years, 6 studies[24,28,33,52,60,63] for 5 years or more, and 2 studies[44,59] reported lifetime PA. Two studies[50,62] had self-reported case confirmation. Two studies[61,63] included less than 100 breast cancer cases. As for menopausal status, 9 studies[24,25,27,36,40,48,51,55,65] studied premenopausal status, 21 studies[7,25,27–30,32–34,36,37,42,45,47,48,50,53,58,59,61,63,65] studied postmenopausal status, and 16 studies[25,35,36,40,43,44,46,47,49,52,56,57,60,62,64,66] studied mixed menopausal status. Nine studies[24,25,29,33,34,38,42,54,63] reported the rate of loss to follow-up, whereas others did not.

Considering the dose–response analyses, we included only those studies that reported PA measured in MET-h/wk. No study was included for occupational activity, and 2 studies[35,37] provided the data for nonoccupational activity. For recreational activity, 4 studies[34,35,38,49] provided the data. Five studies[26,39,42,49,53] provided the data for total activity, but 1 study[42] was deleted because its categories were inconsistent with those of the other 4 studies. Thus, we conducted the dose–response analyses only for recreational activity and total activity.

Primary Results and Heterogeneity

Forest plots for all 38 studies are shown in Figure 2. The overall relative risk (ORR) of breast cancer in the highest category compared with that of the lowest category of PA was 0.87 (95% CI 0.84-0.90). An I^2 of 41.00% indicated moderate heterogeneity in risk between studies. The results are presented in Table 2.

The association between PA and breast cancer risk did not change materially considering age-adjusted model[33,34,36,37,40,42,43,46,51,59,63] (ORR 0.82; 95% CI 0.76-0.88; I^2 = 58.60%). The risk of studies conducted in North America[7,23–26,29,30,33,34,38,40,42,45–48,57–59,61–64,66] (ORR 0.86; 95% CI 0.83-0.89; I^2 = 40.70%) was close to that of studies conducted in Europe[27,28,31,32,35,50–52,56,60,65] (ORR 0.89; 95% CI 0.85-0.93; I^2 = 0.00%).

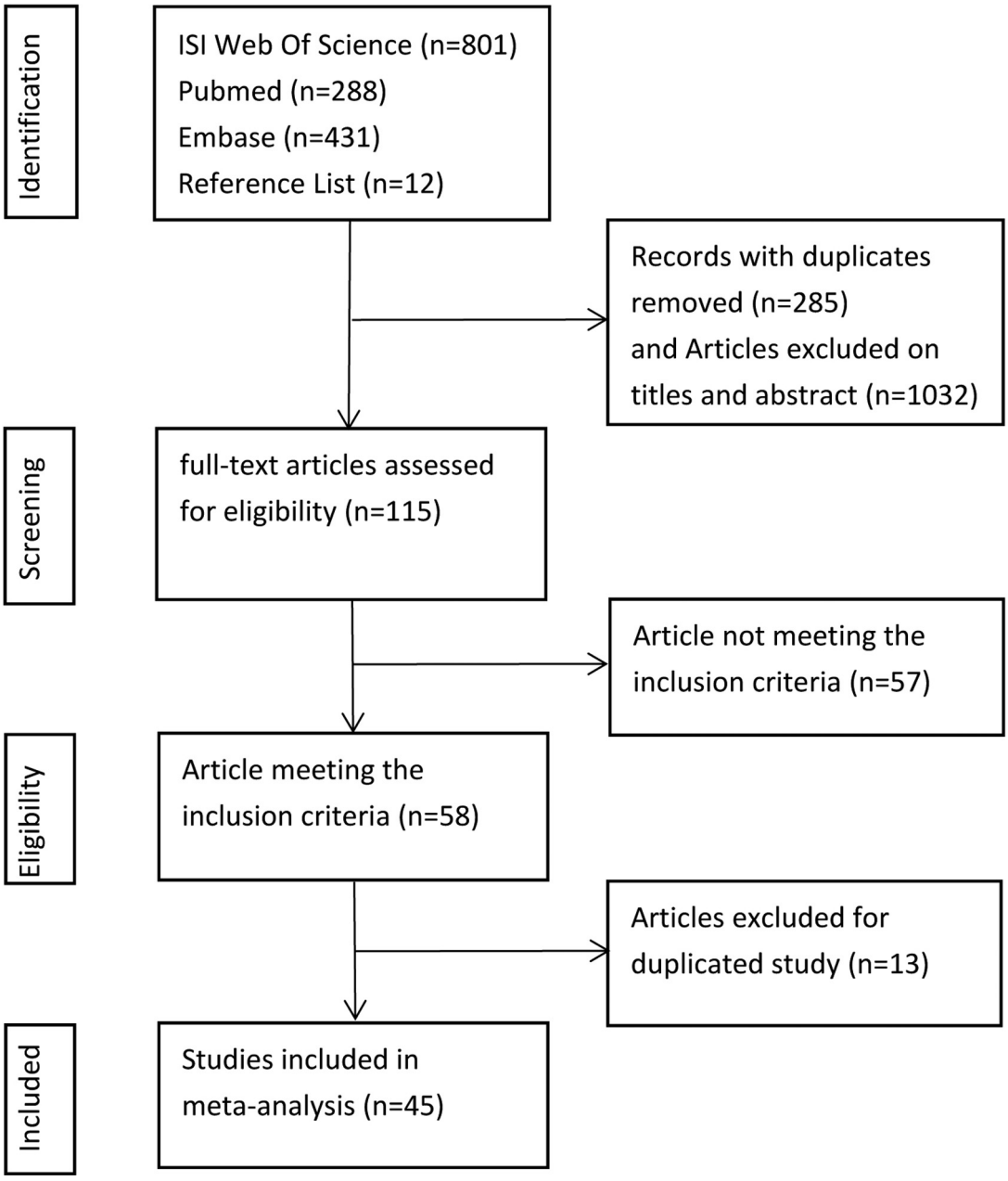

Fig. 1 – Flowchart of literature search strategy to identify cohort studies on breast cancer risk and PA. PA indicates physical activity.

Stronger association of PA with breast cancer risk was found for the Asian cohort[36,37,43] (ORR 0.76; 95% CI 0.63-0.89; $I^2 = 79.00\%$).

Risk reductions of follow-up time of more than 10 years[7,24–26,28,29,34–36,42,43,45–48,50,52,56,57,60–66] (ORR 0.85; 95% CI 0.82-0.87; $I^2 = 47.50\%$) were more pronouncing than those of follow-up time of less than 10 years[23,27,30–33,37,38,40,51,58,59] (ORR 0.89; 95% CI 0.85-0.93; $I^2 = 00.00\%$).

The duration of different PA exposures also reduces the risk of breast cancer. The risk of breast cancer was significantly lower in people with exposure periods longer than 1 year and less than 5 years (ORR 0.62; 95% CI 0.46-0.78), followed by those with lifetime activity (ORR 0.81; 95% CI 0.69-0.93). The ORR of the people with exposure duration equal to or less than 1 year was 0.87 (95% CI 0.84-0.91), and for subjects who have been exposed for 5 years or longer, it was 0.87 (95% CI 0.82-0.92).

Moderate between-study heterogeneity ($I^2 < 50\%$) was found in menopausal status. Studies of different menopausal status suggest that risk reduction was more significant with premenopausal status (ORR 0.83; 95% CI 0.79-0.87; $I^2 = 35.60\%$) than with postmenopausal status (ORR 0.91; 95% CI 0.85-0.97; $I^2 = 23.30\%$), but menopausal status of 27.34% breast cancer cases was unknown.

Similar results were found for breast cancer risk with total PA[7,26,35,36,40,42,66] (ORR 0.87; 95% CI 0.81-0.93; $I^2 = 18.00\%$), recreational PA[23–25,29–36,38,43,46,48,51,56,57,59,60,65] (ORR 0.88; 95% CI 0.85-0.91; $I^2 = 46.30\%$), occupational PA[35,47,52,56,60,65] (ORR 0.91; 95% CI 0.84-0.99; $I^2 = 39.70\%$), and

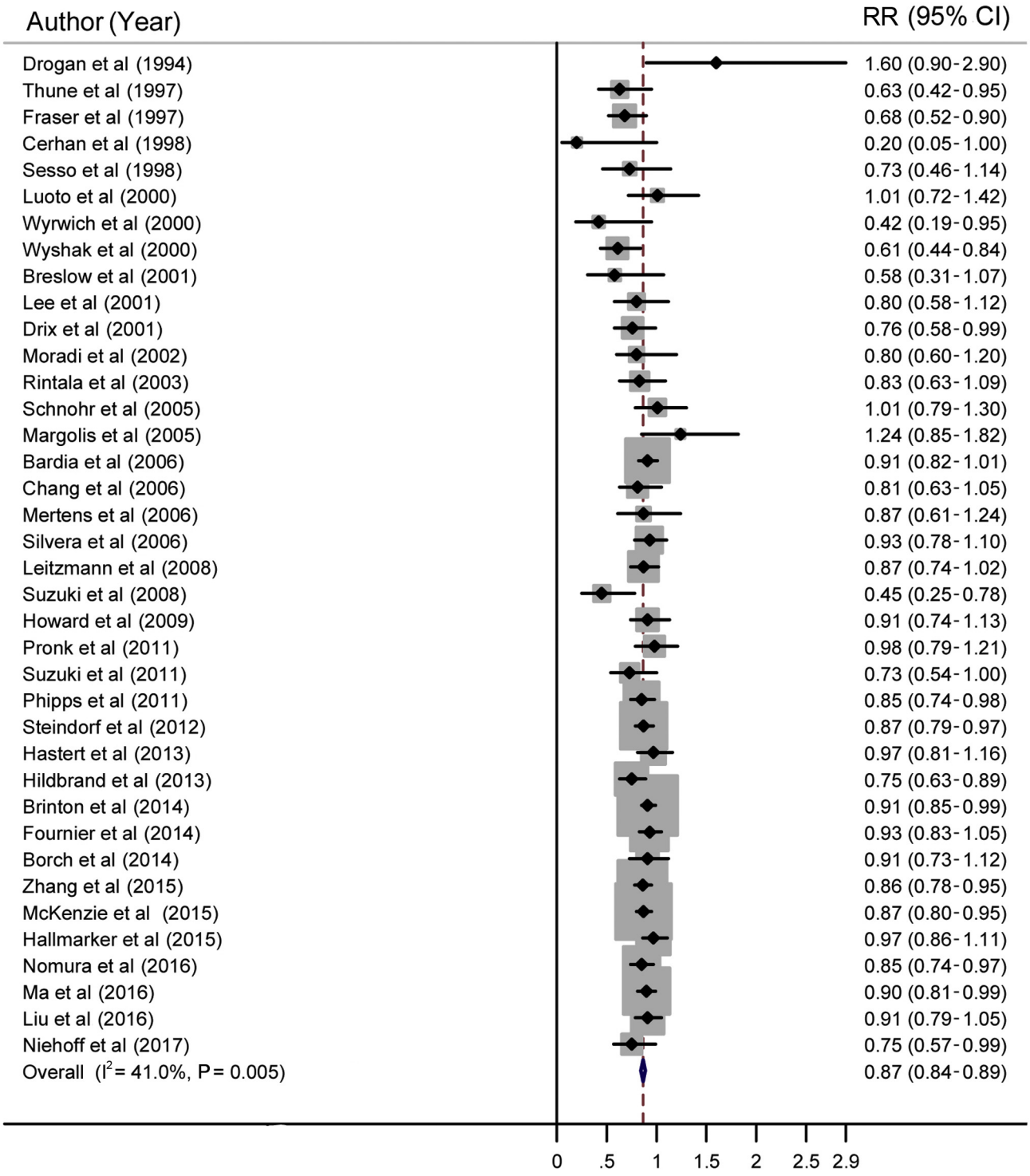

Fig. 2 – Forest plot of breast cancer risk and PA. The black point represents the RR, the solid line represents the range of the CI, and the gray boxes represent the weight of each article. CI indicates confidence interval; PA, physical activity; RR, relative risk.

nonoccupational PA[27,28,37,45,47,50,58,61–64] (ORR 0.87; 95% CI 0.83-0.92; $I^2 = 61.70\%$).

Risk reductions were similar in studies that measured PA in other unit[7,25,27,28,32,40,47,50–52,56–58,61–65] (ORR 0.85; 95% CI 0.81-0.89; $I^2 = 49.50\%$), in hours per week[23,24,33,36,43,46,48,59,66] (ORR 0.86; 95% CI 0.78-0.89; $I^2 = 56.30\%$), and in MET-h/wk[26,29,31,34,35,37,38,42] (ORR 0.87; 95% CI 0.83-0.91; $I^2 = 0.00\%$), but the reduction was the highest in studies that measured PA in times per week[30,45,60] (ORR 0.91; 95% CI 0.86-0.97; $I^2 = 0.00\%$).

The ORR of subjects[31,36,41,42,44,46,54,55,57,59] with a BMI of less than 25 kg/m^2 (ORR 0.88; 95% CI 0.83-0.93; $I^2 = 47.50\%$) was close to that of subjects[31,36,41,42,44,49,56,57] with a BMI of more than 25 kg/m^2

Table 2 – Pooled measures in subgroup analysis on the relationship between PA and breast cancer.

Variable	Number of studies	Number of breast cancer cases	ORR (95% CI)		I^2
			Fixed-effects model	Random-effects model	
Overall	38	68,416	0.87 (0.84–0.90)	0.85 (0.82–0.89)	41.00%
Age-adjusted RR	11	12,789	0.82 (0.76–0.88)	0.82 (0.73–0.92)	58.60%
Location where the study was conducted					
North America	24	40,468	0.86 (0.83–0.89)	0.84 (0.80–0.88)	40.70%
Europe	11	26,372	0.89 (0.85–0.93)	0.89 (0.85–0.93)	0.00%
Asia	3	1,576	0.76 (0.63–0.89)	0.73 (0.43–1.02)	79.00%
Follow-up years					
>10	26	43,089	0.85 (0.82–0.87)	0.82 (0.77–0.87)	47.50%
<10	12	25,327	0.89 (0.85–0.93)	0.89 (0.85–0.93)	0.00%
The period of life (t) during which PA was performed					
Past t ($t \leq 1$ y)	14	43,168	0.87 (0.84–0.91)	0.87 (0.80–0.91)	22.8%
Past t ($1 < t < 5$ y)	2	526	0.62 (0.46–0.78)	0.62 (0.46–0.78)	0.00%
Past t ($t \geq 5$ y)	6	15,380	0.87 (0.82–0.92)	0.87 (0.77–0.96)	53.10%
Lifetime	2	3,857	0.81 (0.69–0.93)	0.81 (0.69–0.93)	0.00%
Menopausal status					
Premenopausal	9	14,968	0.83 (0.79–0.87)	0.80 (0.75–0.86)	35.60%
Postmenopausal	22	40,060	0.91 (0.85–0.97)	0.91 (0.82–0.99)	23.30%
Mixed menopausal	16	20,706	0.87 (0.84–0.88)	0.85 (0.81–0.90)	41.50%
PA type					
Total	7	13,460	0.87 (0.81–0.93)	0.87 (0.80–0.94)	18.00%
Recreational	21	47,156	0.88 (0.85–0.91)	0.86 (0.81–0.90)	46.30%
Occupational	6	10,030	0.91 (0.84–0.99)	0.86 (0.73–0.99)	39.70%
Nonoccupational	11	15,975	0.87 (0.83–0.92)	0.84 (0.74–0.93)	61.70%
Quantification of PA					
Other unit	18	19,957	0.85 (0.81–0.89)	0.82 (0.75–0.90)	49.50%
Hours per week	9	13,919	0.86 (0.78–0.89)	0.80 (0.71–0.89)	56.30%
Frequency (times/wk)	3	10,264	0.91 (0.86–0.97)	0.91 (0.86–0.97)	0.00%
MET (h/wk)	8	24,276	0.87 (0.83–0.91)	0.87 (0.83–0.91)	0.00%
BMI*					
>25 kg/m^2	8	6,778	0.87 (0.77–0.97)	0.85 (0.72–0.98)	35.10%
≤25 kg/m^2	10	9,417	0.88 (0.83–0.93)	0.86 (0.78–0.95)	47.50%
BMI adjusted/nonadjusted					
RR with BMI adjusted	25	48,277	0.87 (0.84–0.90)	0.85 (0.81–0.89)	38.00%
RR with BMI unadjusted	13	20,139	0.87 (0.82–0.91)	0.85 (0.77–0.93)	50.00%

BMI indicates body mass index; CI, confidence interval; MET, metabolic equivalent of energy; ORR, overall relative risk; PA, physical activity; RR, relative risk.

* Data were collected before PA exposure assessment.

(ORR 0.87; 95% CI 0.77-0.97; $I^2 = 35.10\%$). The ORR for studies with multivariate-adjusted model without adjustment for BMI was 0.87[7,23,26-28,33,37,47,52,56,59,62,63] (95% CI 0.82-0.91; $I^2 = 50.00\%$), and that for studies with multivariate-adjusted model with adjustment for BMI[24,25,29–32,34–36,38,40,42,43,45,46,48,50,51,57,58,60,61,64–66] was 0.87 (95% CI 0.84-0.90; $I^2 = 38.00\%$).

Meta-regression analysis was performed on the following: the location where the study was conducted, PA type, menopausal status, the period of life for which PA was performed, and whether BMI was adjusted. The results showed that these covariates are not related to heterogeneity ($P > .050$).

Sensitivity Analysis and Publication Bias

Sensitivity analysis showed that no individual study had excessive influence on the pooled effect between breast cancer risk and PA. Thirty-eight articles were included; publication bias was tested by the Egger test. The Egger test (Fig. 3) showed no evidence of significant publication bias for the analysis between breast cancer risk and PA ($P = .106$).

Dose–Response Relationship Curves

Dose–response analyses were performed with 7 studies[26,34,35,38,42,49,53] that measured PA in MET-h/wk. Four studies[26,42,49,53] included total PA, 4 studies[34,35,38,49] recreational PA, and 1 study[49] both total PA and recreational PA.

Recreational PA dose–response analyses

These studies were heterogeneous (P<.050), and so we chose the random-effects dose–response model. A linear relationship was found between breast cancer risk and recreational PA (P for non-linearity=.800), and the ORR was reduced by 3% (ORR 0.97; 95% CI 0.95-0.99) for every 10 MET-h/wk increment, with a 9% (ORR 0.91; 95% CI 0.85-0.98) reduction for every 30 MET-h/wk increment and a 15% (ORR 0.85; 95% CI 0.76-0.96) reduction for every 50 MET-h/wk increment (Fig. 4A).

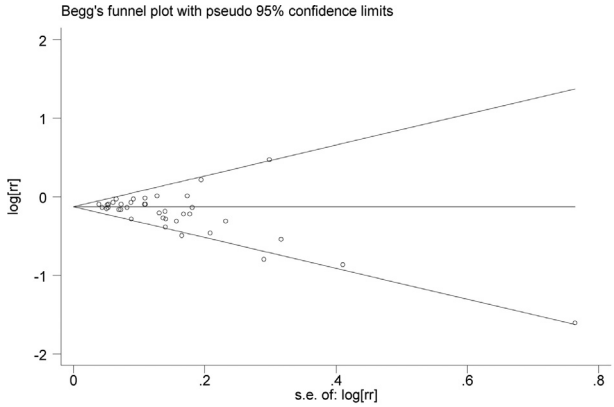

Fig. 3 – Egger test for analysis of breast cancer risk and PA. PA indicates physical activity.

Total PA dose–response analyses

The studies included were homogeneous (P>.050), and so we chose the fixed-effects dose–response model. A linear relationship was found between breast cancer risk and total PA (*P* for nonlinearity=.890), and the risk of breast cancer was reduced by 2% (ORR 0.98; 95% CI 0.97-0.99) for every 10 MET-h/wk increment, with a 6% (ORR 0.94; 95% CI 0.91-0.97) reduction for every 30 MET-h/wk increment and a 10% (ORR 0.90; 95% CI 0.85-0.95) reduction for every 50 MET-h/wk increment (Fig. 4B).

Discussion

The results of this meta-analysis are based on a rigorous and standardized analysis of the available literature on PA and breast cancer risk.

In the development of breast cancer, endogenous sex hormones exercise critical functions[67] because evidences from the association with menstrual cycle and reproductive characteristics are significant, such as age at menarche, menopausal status, and first birth.[68,69] One study[13] suggested that the most obvious risk reduction was in the postmenopausal state. Another study found that PA can reduce serum levels of these hormones in postmenopausal women.[70] Our results suggest that the reduction in breast cancer risk in premenopausal state was greater than in postmenopausal state. The bias may be caused by a large proportion (42%) of women with unknown menopausal status. Many studies did not report results according to menopausal status.

It is still unclear as to which PA may protect against breast cancer. Studies of occupational PA have produced inconsistent results. Kullberg et al[71] concluded that reproductive and lifestyle factors explained only a minor part of the increased risk of breast cancer in white-collar workers. Ekenga et al[72] found that occupational PA was associated with a reduced risk of breast cancer, and associations were the strongest among overweight (HR 0.64; 95% CI 0.42-0.98) and postmenopausal (HR 0.67; 95% CI 0.45-0.98) women. Moradi et al[56] found that recent recreational activity was associated with a reduced risk of postmenopausal breast cancer in contrast to activity from age 18 to 30 y and during childhood. A weaker association between different kinds of PA and breast cancer risk was found. Occupational PA reduced the risk by only 9%, whereas nonoccupational PA reduced the risk by 13%. Risk reduction for recreational PA was 12%, and for total PA 13%. Risk reduction for nonoccupational PA was close to that for recreational PA, possibly because of the overlapping of types of nonoccupational PA and recreational PA, such as household activities belonged to both nonoccupational PA and recreational PA, and so overlapping data were generated.

One systematic review found an inverse association for activity done for less than 25 years, 25 to 50 years, more than 50 years, and through follow-up.[73] We also found an inverse association in different groups of follow-up. For the current stage of methodology development of meta-analysis, there is still no good way to deal with the different follow-up time periods among different studies. So we chose the period of life (t) during which PA was performed to evaluate time effect. The period of life (t) during which PA was performed was also important for the occurrence of breast cancer. In our research, the crucial finding was that for those who were exposed for 1 to 5 years in the past, the risk was reduced to 38%; for people who were exposed for lifetime, it was also reduced by 19%. Margolis et al[51] found that only a change from being physically inactive to active from age 30 years to enrollment was beneficial. Exposure at different times may lead to differences in the body's endocrine conditions, especially sex hormones. We speculate that exposure to PA during a specific period will reduce the risk of breast cancer more effectively.

Physical inactivity usually leads to obesity, and obesity adds the risk of both breast cancer occurrence and mortality.[74,75] Obesity has a complex relationship with breast cancer risk that differs in premenopausal and postmenopausal women. In premenopausal women, obesity is associated with a lower risk of breast cancer[10,11] possibly because of lower sex hormone

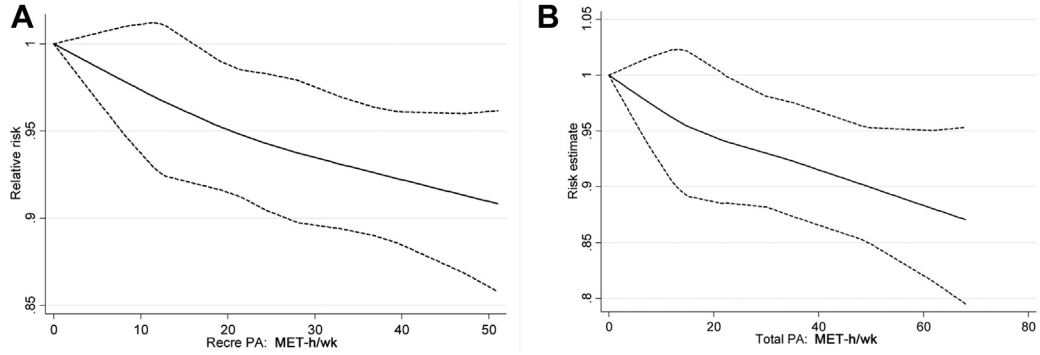

Fig. 4 – The dose–response analyses between breast cancer risk and PA with restricted cubic splines in a multivariate random-effects (A)/fixed-effects (B) dose–response model in studies that measured PA in MET-h/wk. The solid line represents the estimate RR and the long dashed line represents its 95% CI. MET indicates metabolic equivalent of energy; PA, physical activity; Recrea, recreational; RR, relative risk.

concentrations[76] in obese premenopausal women. Weight gain as an adult is also positively associated with risk of postmenopausal breast cancer, with a 6% increase in risk for every 5 kg gained since the age of 20 years (HR 1.06; 95% CI 1.01-1.11).[77] Nevertheless, in another study, in postmenopausal women, particularly the elderly, the association is a positive one, consistent with obesity being a risk factor.[8] In our meta-analysis, the effect of PA does not seem to be modified by BMI, and the ORR for a BMI of more than 25 is also close to the ORR for a BMI of less than 25. The biological mechanisms of how PA reduces breast cancer risk may include adiposity, sex hormones, insulin resistance, adipokine, and inflammatory markers.[78] The exact mechanism is unclear, but Neilson et al[12] provided a plausible mechanism that relating PA to postmenopausal breast cancer risk is through weight control. A similar independence of risk associated with PA was found by the International Agency for Research on Cancer review.[5] A dose–response analysis 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).[79] Unfortunately, weight changes during the follow-up were not reported in most of these studies, and thus we did not evaluate the combined effect of PA and weight changes on the risk of breast cancer.

We found only a linear dose–response relationship, and suggested that increment in PA level could lead to reduction in the risk of breast cancer; this result was consistent with those of other systematic reviews.[73,80] A study[77] shows that women who exercised more than 30.9 MET-h/wk had a 21% decreased risk of breast cancer compared with women who exercised less than 3 MET-h/wk, most evident in premenopausal women (HR 0.62; 95% CI 0.43-0.90). Nevertheless, Neilson et al[12] also found a J-type curve, which is an important issue in devising any public health recommendations. The reasons for why we did not arrive at a J-type curve are as follows: the inclusion of different standards in the literature led to different degrees of PA in the included articles, and the article with the J-curve included only moderate to vigorous PA, whereas this systematic review included PA level ranging from 0 to 68 MET-h/wk. Therefore, it is necessary to study the effect of the different levels of PA on the risk of breast cancer, especially moderate to vigorous PA. At the same time, it is suggested that the classification of PA strictly follows international standards.

Strengths of the Study

Strengths of our analyses include that we combined data from 38 cohort study reports, many of which were large. Studies of breast cancer were together based on approximately 2.53 million participants, including 68 416 cases of breast cancer. Therefore, the meta-analyses should provide sufficiently reliable estimates of RR associated with light and vigorous PA. We chose the NOS for evaluating study quality; the NOS scores for all the articles were more than 5. We included only prospective studies to avoid biases associated with retrospective designs (such as case-control studies), and there was no significant evidence of publication bias in our study (*P* for the Egger test=.106). Moderate heterogeneity in all studies suggested that most studies consistently found a result: the levels of PA increment associated with reduction in breast cancer risk. We reported results of subgroup analysis separately, which includes the location where the study was conducted, follow-up years, menopausal status, types of PA, and so on. Importantly, the results showed consistency among all subgroups.

Limitations of the Study

This meta-analysis has several limitations. First, PA was more likely to be ascertained using self-administered questionnaires, which are prone to misreporting. Second, we did not have individual-level data for study participants (many studies were old), and so we could not use raw data, whereas having raw data would allow more sophisticated models between risk of breast cancer and PA to be examined (with increased power for these analyses). Third, although subgroup analysis was done, we did not find the source of heterogeneity. It required further exploration. Fourth, because of insufficient literature, we did not conduct dose–response analyses of recreational and occupational PA alone, and nor did we conduct dose–response analyses for premenopausal and postmenopausal status separately.

Conclusions

Our systematic review strengthens the evidence that an inverse correlation existed between PA and breast cancer risk. The next task is to study which range (or intensity) of PA is most significant for reducing the risk of breast cancer and how much PA is needed in your life and even to organize large-population randomized trials based on medical ethics, which would encourage and urge people to do PA and therefore provide more realistic data and minimize bias. Besides PA, we can explore the impact of other lifestyle factors on breast cancer risk, such as tea and alcohol consumption and smoking and sleep duration, and achieve the goal of breast cancer prevention by controlling these factors.

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