Second revised version

Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies

Short title: Physical activity and breast cancer risk

Cécile Pizot [2], Mathieu Boniol [1,2], Patrick Mullie [2,3], Alice Koechlin [1,2], Magali Boniol [2], Peter Boyle [1,2] and Philippe Autier [1,2]

1. University of Strathclyde Institute of Global Public Health at iPRI, Allée Claude Debussy, Ecully (Lyon), France
2. International Prevention Research Institute, 95 cours Lafayette, 69006 Lyon, France
3. Faculty of Physical Education and Physiotherapy, Pleinstraat 2, 1050 Brussels, Belgium

Correspondence: Philippe Autier, University of Strathclyde Institute of Global Public Health at iPRI, Espace Européen, Building G, Allée Claude Debussy, 69130 Lyon Ouest Ecully, France; Email: philippe.autier@i-pri.org; Tel: +33 (0)4 72 17 11 99; Fax: +33(0)4 72 17 11 90.

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Abstract

Background: Lower risk of breast cancer has been reported among physically active women, but the risk in women using hormone replacement therapy (HRT) appears to be higher. We quantified the association between physical activity and breast cancer, and we examined the influence that HRT use and other risk factors had on this association.

Methods: After a systematic literature search, prospective studies were meta-analysed using random-effect models applied on highest vs. lowest level of physical activity. Dose-response analyses were conducted with studies reporting physical activity either in hours/week or in hours of metabolic equivalent per week (MET-h/week).

Results: The literature search identified 38 independent prospective studies published between 1987 and 2014 that included 116,304 breast cancer cases. Compared to the lowest level of physical activity, the highest level was associated with a summary relative risk (SRR) of 0.88 (95% CI (0.85, 0.90)) for all breast cancer, 0.89 (95%CI (0.83, 0.95)) for ER+/PR+ breast cancer and 0.80 (95%CI (0.69, 0.92)) for ER-/PR- breast cancer. Risk reductions were not influenced by the type of physical activity (occupational or non-occupational), adiposity, and menopausal status. Risk reductions increased with increasing amounts of physical activity, without threshold effect. In six studies, the SRR was 0.78 (95% CI (0.70, 0.87)) in women who never used HRT and 0.97 (95% CI (0.88, 1.07)) in women who ever used HRT, without heterogeneity in results. Findings indicate that a physically inactive women engaging in at least 150 minutes per week of vigorous physical activity would reduce their lifetime risk of breast cancer by 9%, a reduction that might be two times greater in women who never used HRT. **Conclusion:** Increasing physical activity is associated with meaningful reductions in the risk of breast cancer, but in women who ever used HRT, the preventative effect of physical activity seems to be cancelled out.

Keywords: physical activity; prospective studies; breast cancer; HRT; meta-analysis.

Introduction

Breast cancer is the commonest incident form of cancer in women worldwide which is responsible for approximately 1.7 million new cases in 2012 [1]. The ageing of the world's population, the notable increase in life expectancy, the sharp tendency towards adoption of a westernized lifestyle including lower fertility and sedentary, shorter duration of breastfeeding, and the raising prevalence of obese and diabetic subjects, represent an accumulation of factors known to be associated with breast cancer that will contribute to the continual increase in the global burden of this cancer [2]. A public health priority is the identification of environmental or lifestyle factors whose modification could lead to reductions in breast cancer occurrence. Adiposity, alcohol consumption, and physical inactivity are modifiable risk factors that would contribute to 25% of breast cancer cases in France, 33% in USA, 38% in the United Kingdom, 22% in Brazil and 11% in China [3, 4]. The preventive potential of physical activity was unveiled by a small study on 69 breast cancers that found a 44% (95% CI (0, 77)) reduced rate of breast cancer among female college athletes [5]. Since then, epidemiological studies have generally corroborated the inverse association between physical activity and breast cancer [6, 7]. However, the magnitude of the reduction in breast cancer risk associated with physical activity remains imprecise because of the variability in the way epidemiological studies measured physical activity, analysed data and reported results.

Higher levels of circulating oestrogen and androgen are related to higher breast cancer risk [8-10], and studies among postmenopausal women consistently showed that physical activity can reduce serum levels of these hormones [11, 12]. Use of hormone replacement therapy (HRT) increases levels of circulating sex-hormones and the risk of breast cancer [13, 14]. A question is thus whether HRT use could influence the preventative effect of physical activity.

In this study, we quantified the association between physical activity and breast cancer risk in prospective studies, exploring in more depth the influence that exposure assessment and breast cancer risk factors, especially HRT use, could have on this association. Risk reductions associated with measurable amounts of physical activity were also evaluated.

Materials and Methods

Literature search and study selection

A systematic literature search and quantitative analysis was conducted following PRISMA guidelines [15]. This search was restricted to articles published in English language up to November 2014 and available in the following database: Ovid MEDLINE database, ISI Web of Science, Science Citation Index Expanded, and PUBMED. A combination of key words and MesH index terms was used including "breast neoplasm" or "breast cancer", "physical activity" or "physical exercise" or "motor activity", "cohort study" or "prospective study" or "longitudinal study". The reference lists of retrieved articles were also hand searched. Eligible articles for this study had to (i) report data on incident cases of breast cancer; (ii) report measurement of physical activity, being occupational and/or non-occupational; (iii) have a prospective design. As case-control studies are more prone to recall and selection biases, and thus to provide less accurate risk estimates, this systematic review focused only on studies with prospective design.

Titles and abstracts were screened for eligibility. Full copies of eligible articles were retrieved and fully read by at least two co-authors. When several articles were published on the same study, the most recent publication was selected, except for those data that were relevant for sub-analyses.

Data extraction

Extraction of main study characteristics, exposure assessment and relative risks was done by one co-author in a pre-defined database. The resulting table was checked by another author and by a statistician. All relative risks (RR) with the corresponding 95% confidence interval (CI) were extracted for each category of physical activity. As a rule, we selected the most adjusted RRs associated with the most comprehensive measure of physical activity that was often labelled as "total physical activity".

Statistical Methods

Various risk estimates (RR) and their 95% CI were transformed into log (RR) and their corresponding variances were computed. When no RR was reported, tabular data were used to calculate the crude estimates and 95% CIs. In the case of a RR reported separately by type of physical activity (i.e., occupational or non-occupational activity) or by menopausal status, a fixed-effect modelling was used to combine all the RRs in order to get a global result for the main analysis (Table S1). From the transformed data, summary relative risks (SRR) were computed using a random effects model [16] and the confidence intervals were based on the t-distribution. As physical activity assessment and reporting of results were very heterogeneous across studies, breast cancer risk associated with the highest level of physical activity was compared with the lowest level of physical activity.

Heterogeneity across studies was evaluated by the I^2 statistic, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance [17]. Three tests for publication bias were performed, the Begg test [18], the Egger test [19] and the Macaskill test [20].

Subgroup meta-analyses were conducted according to the study location, the period of study (before 1989 vs. after 1989; based on the mid-year of each cohort), the type of physical activity (non-occupational vs. occupational), and the metric used to quantify physical activity (MET-h/week, hours/week or no quantitative measure). Regarding hormone receptor status, results for ER+ and triple negative (ER-/PR-/HER2-) tumours were used as approximation of ER+/PR+ and ER-/PR- tumours respectively, in two studies [21, 22]. Stratified meta-analyses were performed considering risk factors for breast cancer, including menopausal status, HRT use, and adiposity. For adiposity, RRs for the most extreme BMI categories reported by articles were used.

A dose-response analysis was conducted with studies reporting physical activity either in hours/week or in MET-h/week. The great variability in MET-h/weeks reported by studies precluded the possibility to perform a dose-response analysis as proposed by Greenland and Longneker [23]. We thus opted for a non-parametric approach in which ranks of physical activity levels expressed as MET-h/week or as hours/week were re-scaled so that exposure categories of all studies had the same range of values. Each study was scaled to share the first (reference) and last category of physical activity, whatever the number of categories defined by studies. Because there were three, four and five possible categories of MET-h/week, cut-points were arbitrarily assigned *a priori* at 0, 1, 1.33, 2, 2.67, 3 and 4. Hence, if in a study, there were three categories of MET-h/week, category limits were 0 (reference), 2 and 4. The same method was applied to the hours/week analysis but six categories of physical activity were used and cut-points were assigned at 0, 1, 1.25, 1.67, 2, 2.5, 3, 3.33, 3.75, 4 and 5. Then, RRs reported by studies were plotted against re-scaled exposure categories. In order to estimate a summary slope, a linear regression of the log (RR) according to physical activity categories, weighted by the inverse variance of log (RR), was conducted for each study. Then, a meta-analysis of the slopes of each linear model was performed using a random-effect modelling. All the analyses were carried out in programming language R (version 3.1.2, GNU General Public License, 2014).

Results

Study selection and description

The literature search identified 928 potentially relevant studies, of which 60 met the inclusion criteria (Figure 1). Among the eligible studies, 22 were further excluded as they were duplicates of main or most recent articles (Table S2) leaving 38 studies in the final analysis. However, nine duplicate studies were included in stratified analyses as they provided results that were not reported in main or most recent articles. Selected and duplicate articles with relevant data are summarized in Table 1. [21, 22, 24-68]

Studies included a total of 4,124,275 women of which 116,304 (2.8%) were diagnosed with a breast cancer during the study period. Most of these cancers were invasive but a small number of *in-situ* breast cancer were also included in few studies (see Table S3 for the type of cancer included in each study). Twelve percent of breast cancer cases were pre-menopausal, 45% were post-menopausal, and menopausal status was unknown for 43%.

The way physical activity was assessed and reported varied across studies (Table 1 and Table S4). In most studies (24), physical activity related to the month(s) or year(s) preceding inclusion in the cohort. Three studies evaluated occupational physical activity only, 22 studies assessed non-occupational physical activity only, seven studies assessed both and reported results for each type of activity, and six studies assessed total physical activity without breakdown by type of physical activity.

Eight studies reported physical activity measured in MET-h/week, nine reported duration of physical activity per day or per week and three reported in both units. Eighteen studies classified physical activity in discrete categories without use of measurement units to describe category boundaries. The lowest level of physical activity usually corresponded to being inactive, including sedentary and sitting.

Meta-analysis of all studies

For all 38 studies, the SRR of breast cancer in the highest compared with the lowest category of physical activity was 0.88 (95% CI (0.85, 0.90)) (Figure 2). The I^2 of 29% indicates moderate heterogeneity in risks between studies, mainly due to the five studies that found an increased risk. Careful reading of the five studies provided no clue on the reasons possibly underlying these findings, except Dorgan et al. 1994 [25] that specified that less than 5% of women reported regular vigorous physical activity.

The SRR was not materially altered when meta-analysis was restricted to the 23 studies that assessed physical activity in the year(s) preceding inclusion in cohorts, or to the 18 studies that included invasive cancer only, or after exclusion of the Moradi et al. 1999 [31] study that included 37% of all breast cancer patients in the meta-analysis (data not shown).

Stratified analysis

The location of studies, the BMI of women or the adjustment for BMI did not influence risk reductions associated with physical activity (Figure 3). Risk reductions were similar in pre- and post-menopausal women, but menopausal status was unknown for 43% of women.

A greater reduction of breast cancer risk was observed in studies conducted before 1989 than after, but all the heterogeneity in results was confined to studies conducted before 1989. The SRR for studies conducted before 1989 was 0.78 (95%CI (0.69, 0.88)) when the Moradi et al. 1999 [31] study was excluded.

Risk reductions were greater in studies that measured physical activity in hours/week (19% reduction) than in MET-h/week (13% reduction) or in other units (11% reduction). The difference in risk reduction was essentially due to vigorous physical activity (e.g., activities like jogging associated with sweating) being more frequently reported in hours/weeks while reporting in MET-h/week generally encompassed physical activities of any magnitude, from housekeeping to strenuous activity.

Studies that measured both types of physical activity suggest that risk reductions were slightly more pronounced with non-occupational than with occupational physical activity.

Regarding hormone receptor status, one study [38] reported risks for ER+/PR+ tumours but not for other tumours. For this reason, 10 studies were used to compute a SRR for ER+/PR+ tumours and nine studies were used for ER-/PR- tumours. Reduction in breast cancer risk was more pronounced for ER-/PR- tumours (SRR=0.80) than for ER+/PR+ tumours (SRR=0.89).

HRT use was reported in 19 of the 36 studies conducted in the USA and in Europe. Sixty one percent of women reported never use of HRT and 39% reported ever use of HRT (i.e., current or past use). This utilization frequency remains the same in the six studies that examined the influence of physical activity according to HRT use (Table 2).[35, 42, 50, 55, 56, 66] Although the SRR for the six studies was 0.88, breast cancer relative risks associated with highest level of physical activity were always smaller for never users of HRT than for ever users. Overall, it seemed that the entire preventive effect was confined to women who never used HRT (SRR=0.78) as no risk reduction was noticeable in women who reported ever use of HRT (SRR=0.97). The absence of overlapping between the confidence interval around SRRs for never and ever users of HRT indicates statistically significant effect modification (confirmed by meta-regression: $p<0.05$). There was no heterogeneity in results across the six studies.

Dose-response analysis

Dose-response analyses were performed with the 11 studies that reported physical activity in MET-h/week and the 11 studies that reported duration of physical activity in hours/week. Significant dose-response relationships were found ($p <0.0001$) between amounts of physical activity and breast cancer risk indicating steady reductions in risk with increasing physical activity, without evidence for a threshold (Figure 4).

The reporting in MET-h/week usually encompassed all activities, being vigorous or not. Moreover, list of activities for which MET was estimated has continuously expended [69-71]. Consequently, the level of detail collected on physical activity varied across studies and scales of MET-h/week were very heterogeneous. For instance, Phipps et al. 2011 [21] used four categories of exposure ranging from 0 to ≥16.5 MET-h/week, whereas Leitzmann et al. 2008 [52] used five categories of physical activity ranging from 105 to 721 MET-h/week.

Reporting of physical activity in hours/week was mostly related to vigorous physical activity only. Categories in hours/week were frequently imbalanced, with extreme categories populated with few women having unusually high levels of physical activity (Table 3) [22, 37, 47, 49-51, 53-55, 57, 66]. To obtain more realistic data, the two highest levels of vigorous physical activity were combined and RR were recomputed using a fixed-effect meta-analysis, in three studies [22, 50, 55]. After these modifications of exposure categories, the differences between lowest and highest levels of physical activity ranged from 3 to 7 hours/week with a mean of 5 hours/week. Women spending at least 5 hours/week of mainly vigorous activity had an 18% (95%CI (13, 23)) reduction in breast cancer risk compared with women who had no or limited vigorous physical activity. 42% of women included in these 11 studies ever used HRT and assuming that physical activity does not reduce the risk of breast cancer in women who ever used HRT, it is possible to estimate the risk reduction associated with 5hours/week or more of mainly vigorous physical activity in never HRT users (i.e., from resolution of the equation $0.42\ RR_{everHRT} + 0.58*RR_{neverHRT} = 0.82$, assuming $RR_{everHRT} = 1$). A sustained change from being physically inactive to engaging in 5 hours/week or more of mainly vigorous physical activity could lead to a 31% (95%CI (22, 40)) risk reduction in women who never used HRT.

Discussion

This meta-analysis demonstrates three important findings. First, increased levels of physical activity lead to reductions in the risk of breast cancer irrespective of the type of physical activity, place of residence, adiposity, menopausal status, and the hormone receptor status of tumours. Second, breast cancer risk seems to decline with increasing physical activity, without a threshold effect. Third, women who ever used HRT had no reduction of breast cancer risk associated with physical activity. Despite limitations in quantification and reporting of exposure, heterogeneity in study results was moderate suggesting that most studies consistently found reduced risks of breast cancer associated with increasing levels of reported physical activity.

This meta-analysis has several limitations. First, dose-response meta-analysis using all studies was not performed because quantification and reporting of physical activity was too heterogeneous across studies. If in most studies the lowest level of physical activity coincided with sedentary, it was often difficult to figure out the meaning, in term of quantity, of levels labelled as "moderate" or "high" physical activity. Second, inclusion of *in-situ* breast cancer could have weakened the preventive effect of physical activity. Four studies that examined risk of *in-situ* breast cancer in relation to physical activity found no or equivocal association [51, 57, 72, 73]. However, the meta-analysis restricted to studies that included invasive cancer only showed no difference in SRR. Third, stratified results on menopausal status could be biased as menopausal status of women was unknown in 43% of women and many studies did not report results according to menopausal status.

Four, the result related to HRT use could arise from selection bias since only six studies examined the influence of physical activity according to HRT use. Moreover, it is known that the HRT-induced risk of breast cancer steadily vanishes in the 5-7 years after HRT use discontinuation but, for past users, data on time since last HRT use were not available in publications. However, results of the six studies were highly consistent, there was no evidence of heterogeneity, and the 95% CI around SRRs for ever and for never HRT use did not overlap. Therefore, our study raises the hypothesis that HRT use could nullify the protection conferred by physical activity against breast cancer. This hypothesis is supported by knowledge that a steroid-hormone pathway may play a role in the association between physical activity and breast cancer risk [8-10] and that physical activity can reduce serum levels of these hormones in postmenopausal women [11, 12]. Hence, if physically active women have a reduced risk of breast cancer risk through reductions of circulating oestrogens, then HRT use would cancel out this effect because of re-establishment of oestrogen blood concentrations as if women were physically inactive. Moreover, breast cancers induced by HRT use are more frequently ER+/PR+ than other breast cancers [74-76] which could explain the smaller risk reduction obtained for ER+/PR+ than for ER-/PR- tumours. HRT use was less prevalent before 1990 than during the 1990 to 2002 period [77], after which dramatic reductions in use occurred following the publication of Women’s Health Initiative trial [13] and the Million Women Study [14] that documented the association between HRT use and breast cancer. Studies on physical activity in the USA and Northern Europe were, in their majority, conducted in the 1990’s when large proportions of peri- and post-menopausal women used HRT over long periods of time. Consequently, massive presence of HRT users in cohorts might have led to underestimation of risk reductions expected with physical activity. It may also explain why risk reductions were of 20% in studies conducted before 1989 and of 11% in more recent studies.

Physical inactivity is usually associated with adiposity, and adiposity is a risk factor for both breast cancer occurrence and mortality [78, 79]. However, the stratified analyses according to women’s BMI or to adjustment for BMI showed no change in SRRs. A similar independence of risk associated with physical activity was found by the IARC review [6]. These results indicate that the protective effect of physical activity would be the same at all levels of overweight and obesity. Nevertheless, independently from adiposity, it is well known that weight gain is an important risk factor for breast cancer in post-menopausal women, especially in women not taking HRT [80]. Physical activity could be critical for preventing weight gain and consequently breast cancer. Unfortunately, most of the studies did not report on weight changes during the follow-up, therefore our meta-analysis could not examine the combined effect of physical activity and weight changes on the risk of breast cancer.

Systemic inflammation is probably a main factor on which physical activity exerts considerable influence. Low grade systemic inflammation is practically always present in obesity, diabetes, sedentary, old age, and is associated with aggressive breast cancer phenotype (e.g., ER-/PR- and triple negative) and poor prognosis [81-83]. Randomized trials have shown that increasing physical activity reduces systemic inflammation [84-86]. The influence on systemic inflammation would explain why physical activity seems capable of reducing the risk of breast cancers whatever the hormone receptor status, the menopausal status and the adiposity of women.

This study indicates that avoidance of sedentary behaviours and promotion of physical activity may contribute to control the increase in breast cancer burden taking place in most populations over the world. However, even in women who never used HRT, substantial amounts of physical activity are needed for expecting 20% or more reductions in breast cancer risk. It is not sure that large proportions of women with no or low level of physical activity would be willing, find the time and have the physical aptitude to engage in at least 5 hours/week of strenuous physical activity on the long term. A more realistic perspective indicated by study findings is that a physically inactive women engaging in at least 150 minutes per week of vigorous physical activity would reduce their lifetime risk of breast cancer by 9%, a reduction that might be two times greater in women who never used HRT. Nonetheless, risk reductions were estimated from observational studies which do not necessarily provide a reliable reflection of actual changes in risk that would be associated with public health actions on decreasing sedentary and increasing physical activity. The time is ripe for organizing large population randomized trials that will better inform on the feasibility of policies encouraging physical activity to prevent breast cancer occurrence. On the other hand, other lifestyle risk factors such as alcohol drinking that are known to be associated with an increased risk of breast cancer should also be considered in strategies aiming at preventing breast cancer.

Conflict of interest statement

None of the authors have any potential conflict of interest to declare in relation to the subject matter of this manuscript.

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Figure captions

Figure 1. Flow chart of the literature search strategy to identify cohort studies on breast cancer risk and physical activity.

Figure 2. Forest plot of meta-analysis of breast cancer risk according to physical activity level in women. Individual studies are represented with their RR and 95% CI (highest versus lowest category of physical activity). The square size is proportional to the variance of the RR and the horizontal lines represent the corresponding 95% CI. Heterogeneity between studies was assessed through Q and I^2 statistics. Publication bias was evaluated using Begg, Egger and Macaskill tests.

Figure 3. Results from stratified analyses.

Figure 4. Dose-response relationship between breast cancer risk and physical activity in studies that measured physical activity in MET-h per week (A) or in hours per week (B).

A. MET-h/week

B. Hours/week

Web extra material

Table S1 – Details on computation and data extraction.

Table S2 – Duplicate studies that were excluded from main analysis.

Table S3 – Breast cancer types included in prospective studies.

Table S4 – Assessment of physical activity in prospective studies (duplicate studies from which some data were used are in light grey)

Tables

Table 1: Main characteristics of cohort studies included in the meta-analysis, ranked by year of publication. Duplicate articles not used for the main meta-analysis but from which selected data were used in sub-analyses are highlighted in grey.

First author, year Country	Study name	No. subjects (No. cancer cases)	Years of follow-up	Age of women	Menopausal status	Type of PA	Period in life for PA	Reporting of PA	Risk factor stratification	BMI adjusted [a]
Paffenbarger, 1987 [24] USA	Alumni from the University of Pennsylvania	4,706 (46)	32	NR	PreM/PostM	Non-occ	Early college	≥5h/wk vs. <5h/wk of sport [b]	-	Nadj
Dorgan, 1994 [25] USA	Framingham Heart Study (FHS)	2,298 (117)	28	35-68	PreM/PostM	Occ and non-occ [c]	Baseline	Index combining hours per day of sedentary, moderate and heavy PA (during work and leisure time)	-	Nadj
Steenland, 1995 [26] [d] USA	National Health and Nutrition Examination Survey I (NHANES I)	NR (163)	16	25-74	PreM/PostM	Occ	Baseline	Little, some, a lot	PostM	Adj
Fraser, 1997 [27] USA	Adventist Health Study	20,341 (218)	6	≥25	PreM/PostM	Occ and non-occ [c]	Baseline	Low, moderate, high	-	Adj/Nadj
Thune, 1997 [28] Norway	National Health Screening Service	25,624 (351)	14	20-54	PreM/PostM	Occ and non-occ	Baseline	Non-occupational: sedentary, moderate, regular exercise; Occupational: sedentary, walking, lifting or heavy manual labor	BMI, PreM/PostM	Adj/Nadj

First author, year Country	Study name	No. subjects (No. cancer cases)	Years of follow-up	Age of women	Menopausal status	Type of PA	Period in life for PA	Reporting of PA	Risk factor stratification	BMI adjusted [a]
Cerhan, 1998 [29] USA	Iowa 65+ Rural Health Study	1,806 (46)	11	65-102	PostM	Non-occ	Baseline	Any disability, inactive, moderately active, highly active (based on 5 questions about non-occupational PA and housework)	PostM	Adj [e]
Sesso, 1998 [30] USA	College Alumni Health Study	1,566 (109)	23	37-69	PreM/PostM	Non-occ	Baseline	Weekly energy expenditure in kcal per week	BMI, PreM/PostM	Adj
Moradi, 1999 [31] Sweden	Swedish Cancer Environment Register III (CERIII)	1,687,174 (43,259) [f]	19	NR	PreM/PostM	Occ	Adult life (1960 and 1970 censuses)	Occupational PA classified as sedentary, light, moderate, high/very high	-	Nadj
Luoto, 2000 [32] Finland	Finish Adult health behaviour survey	30,548 (332 [g])	9	15-64	PreM/PostM	Non-occ	Baseline	Leisure time: <once/wk, once/wk, 2-3 times/wk, daily Commuting to work: work at home, commuting by car, <30 min/day walking/bicycling, ≥30 min/day walking/bicycling	BMI, PreM/PostM	Adj
Wyrwich, 2000 [33] USA	Longitudinal Study on Aging (LSOA)	3,131 (77)	7	70-98	PostM	Non-occ	Baseline	Any disability, inactive, moderate, high	PostM	Adj [e]
Wyshak, 2000 [34] USA	US Alumni	3,908 (175)	15	53 (mean)	PreM/PostM	Non-occ	College	Former athletes versus former non-athletes	-	Nadj
Moore, 2000 [35] [h] USA	Iowa Women's Health Study	37,105 (1,380)	10	55-69	PostM	Non-occ	Baseline	Low, medium, high	BMI, HRT, PostM	Adj/Nadj

First author, year Country	Study name	No. subjects (No. cancer cases)	Years of follow-up	Age of women	Menopausal status	Type of PA	Period in life for PA	Reporting of PA	Risk factor stratification	BMI adjusted [a]
Breslow, 2001 [36] USA	National Health Epidemiologic follow-up study (NHEFS, arised from NHANES I)	6,160 (138)	9	24-75	PreM/PostM	Non-occ	Long term PA (baseline and 10y before)	Low, moderate, high	BMI, PreM/PostM	Adj
Dirx, 2001 [37] The Netherlands	Netherlands Cohort Study (NLCS)	2,924 (1,208)	7	55-69	PostM	Occ and non-occ	Lifetime for occupational PA and baseline for non-occupational PA	Minutes per day for non-occupational PA and kJ/min for occupational PA (energy expenditure)	BMI, PostM	Nadj
Lee, 2001 [38] USA	Women's Health Study (WHS)	39,322 (411)	4	≥45	PreM/PostM	Non-occ	Baseline (past year)	4 categories of energy expended during PA in kJ/week	ER/PR [i], PostM	Adj/Nadj
Moradi, 2002 [39] Sweden	Swedish Twin Registry	9,539 (506)	24	42-70	PreM/PostM	Occ and non-occ	Adult life (25-50 years)	Non-occupational: sedentary, moderate, regular PA; Occupational: Sedentary, active, Strenuous	BMI, PreM/PostM	Nadj
Rintala, 2002 [40] Finland	Finnish citizen	680,000 (17,986)	24	≥25	PreM/PostM	Occ	Baseline, at age 20 and at age 35	Five categories of occupational PA: class 1+2, class 3, class 4, class 5	PreM/PostM	Nadj
McTiernan, 2003 [41] [j] USA	Women Health Initiative (WHI)	74,171 (1,780)	5	50-79	PostM	Non-occ	Baseline	MET-hours per week	BMI, PostM	Adj
Patel, 2003 [42] [k] USA	American Cancer Society Cancer Prevention Study II Nutrition Cohort	72,608 (1,520)	5	50-74	PostM	Non-occ	Baseline (past year)	MET-hours per week	BMI, HRT, PostM	Adj/Nadj [e]

First author, year Country	Study name	No. subjects (No. cancer cases)	Years of follow-up	Age of women	Menopausal status	Type of PA	Period in life for PA	Reporting of PA	Risk factor stratification	BMI adjusted [a]
	(CPS-II nutrition Cohort)									
Rintala, 2003 [43] Finland	Finnish female physical education and language teachers	10,049 (465)	34	>25	PreM/PostM	Occ	Lifetime	Physical education teachers (high lifetime PA) vs. language teachers (low lifetime PA)	PreM/PostM	Nadj
Margolis, 2005 [44] Norway, Sweden	Women's Lifestyle and Health Study	99,504 (1,166)	9	30-49	PreM/PostM	Non-occ	Baseline	5 levels of PA: none, low, moderate, high, vigorous	PreM/PostM	Adj
Schnohr, 2005 [45] Denmark	Copenhagen Centre for Prospective Population Studies	13,216 (417)	14	20-93	PostM	Non-occ	Baseline (past year)	3 levels of PA: low, moderate and vigorous	PostM	Adj/Nadj
Bardia, 2006 [46] USA	Iowa Women's Health Study	41,836 (2,548)	18	55-69	PostM	Non-occ	Baseline	Low, medium, high	ER/PR, PostM	Adj/Nadj
Chang, 2006 [47] USA	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)	27,541 (764)	9 (median 5)	55-74	PostM	Non-occ	Baseline	Hours per week	PostM	Adj/Nadj
Mertens, 2006 [48] USA	Atherosclerosis risk in communities (ARIC)	7,994 (342)	13	45-64	PreM/PostM	Occ and non-occ	Baseline	Quartile of PA based on Baecke indices	PostM	Nadj
Silvera, 2006 [49] Canada	Canadian National Breast Screening Study (NBSS)	40,318 (1,673)	16	40-59	PreM/PostM	Non-occ	Baseline (past one month)	Minutes per day	BMI, PreM/PostM	Adj/Nadj
Tehard, 2006 [50] France	E3N cohort of French teachers (E3N)	90,509 (3,424)	12	40-65	PreM/PostM	Non-occ	Baseline	Total PA in MET-hours per week; Vigorous	BMI, HRT	Adj/Nadj

First author, year Country	Study name	No. subjects (No. cancer cases)	Years of follow-up	Age of women	Menopausal status	Type of PA	Period in life for PA	Reporting of PA	Risk factor stratification	BMI adjusted [a]
								recreational PA in hours per week		
Dallal, 2007 [51] USA	California Teachers Study	110,599 (2,649)	7	20-79	PreM/PostM	Non-occ	Lifetime (between high school and current age)	Hours per week	BMI, ER/PR, PreM/PostM	Adj/Nadj
Leitzmann, 2008 [52] USA	Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP)	32,269 (1,506)	8	40-93	PostM	Occ and non-occ [c]	Baseline (past year)	MET-hours per week	BMI, ER/PR, PostM	Adj/Nadj
Maruti, 2008 [53] [l] USA	Nurses' Health Study II (NHS II)	64,777 (550)	6	33-51	PreM	Non-occ	Adolescence and adult (from age 12 to current age)	Total PA in MET-hours per week; Strenuous activity in hours per week	BMI, ER/PR, PreM	Nadj
Suzuki, 2008 [54] Japan	Japan Collaborative Cohort Study (JACC)	30,157 (207)	12	40-69	PreM/PostM	Occ and non-occ [c]	Baseline	Minutes per day (time spent walking) and hours per week (time spent exercising)	BMI, PreM/PostM	Adj/Nadj
Howard, 2009 [55] USA	U.S. Radiologic Technologists cohort (USRT)	45,631 (864)	9	47	PreM/PostM	Occ and non-occ [c]	Baseline (past year)	Total PA in MET-hours per week; Strenuous exercise in hours per week	HRT, PreM/PostM	Adj/Nadj
Peters, 2009 [56] [m] USA	National Institutes of Health-American Association of Retired Persons Diet and Health	182,862 (5,433)	7	50-71	PostM	Occ and non-occ [c]	Baseline (past year)	Times per week (Inactive, <1/wk, 1-2/wk, 3-4/wk, ≥5/wk)	BMI, ER/PR, HRT, PostM	Adj/Nadj

First author, year Country	**Study name**	**No. subjects (No. cancer cases)**	**Years of follow-up**	**Age of women**	**Menopausal status**	**Type of PA**	**Period in life for PA**	**Reporting of PA**	**Risk factor stratification**	**BMI adjusted [a]**
	Study (NIH-AARP)									
Peters, 2009 [57] [m] USA	National Institutes of Health-American Association of Retired Persons Diet and Health Study (NIH-AARP)	118,899 (3,522)	7	50-71	PostM	Non-occ	Past 10 years	Hours per week	ER/PR [n], PostM	Nadj
George, 2010 [58] [m] USA	National Institutes of Health-American Association of Retired Persons Diet and Health Study (NIH-AARP)	97,039 (2,866)	7	50-71	PostM	Occ	Baseline	5 levels of activity: sitting all day; sitting and a little walking; standing or walking, no lifting; lifting or carrying light loads, or climbing stairs often; heavy lifting or carrying	PostM	Adj
Eliassen, 2010 [59] USA	Nurses' Health Study (NHS)	95,396 (4,782)	20	40-65	PostM	Non-occ	Baseline (past year) and update every 2 or 4 years	MET-hours per week	ER/PR, PostM	Adj/Nadj
Pronk, 2011 [60] China	Shanghai Women's Health Study (SWHS)	73,049 (717)	9	40-70	PreM/PostM	Occ and non-occ	Non-occ PA in past year and 5 years before interview. Lifetime occ PA.	Non-occupational: MET-hours per week per year; Occupational: energy expenditure in kJ per min per year	BMI, PreM/PostM	Nadj

First author, year Country	Study name	No. subjects (No. cancer cases)	Years of follow-up	Age of women	Menopausal status	Type of PA	Period in life for PA	Reporting of PA	Risk factor stratification	BMI adjusted [a]
Phipps, 2011 [21] USA	Women Health Initiative (WHI)	155,723 (2,917)	8	50-79	PostM	Non-occ	Baseline	MET-hours per week	ER/PR [o], PostM	Adj
Suzuki, 2011 [61] Japan	Japan Public Health Center-based Prospective Study (JPHC)	53,578 (652)	15	40-69	PreM/PostM	Occ [p] and non-occ	Baseline and updated 5 years after	MET-hours per day; no data for occupational PA only but for leisure time only (in days per month or per week)	BMI, ER/PR, PreM/PostM	Adj/Nadj
Steindorf, 2013 [62] Europe	European Prospective Investigation into Cancer and Nutrition (EPIC)	257,805 (8,034)	12	35-70	PreM/PostM	Occ and non-occ	Baseline (past year for non-occ PA and current for occ PA)	MET-hours per week for non-occupational PA; 4 categories for occupational PA (sedentary; Standing; Manual and heavy manual; non-worker)	BMI, ER/PR, PreM/PostM	Adj
Hildebrand, 2013 [63] USA	American Cancer Society Cancer Prevention Study II Nutrition Cohort (CPS-II nutrition Cohort)	73,615 (4,760)	17 (median 14)	50-74	PostM	Non-occ	Baseline and updated 3 times during follow-up	MET-hours per week for total non-occupational PA	PostM	Adj [e]
Hastert, 2013 [64] USA	Vitamins and Lifestyle study cohort (VITAL)	30,797 (899)	7	50-76	PostM	Non-occ	Past 10 years	Be physically active vs. be physically inactive according to WCRF/AICR cancer prevention recommendations.	PostM	Adj/Nadj
Rosenberg, 2014 [22] USA	Black Women's Health Study (BWHS)	44,708 (1,364)	16	≥30	PreM/PostM	Non-occ	Baseline (past year)	Hours per week [b]	BMI, ER/PR [o], PreM/PostM	Nadj

First author, year Country	Study name	No. subjects (No. cancer cases)	Years of follow-up	Age of women	Menopausal status	Type of PA	Period in life for PA	Reporting of PA	Risk factor stratification	BMI adjusted [a]
Borch, 2014 [65] [q] Norway	Norwegian Women and Cancer Study (NOWAC)	80,202 (1,767)	8	34-70	PostM	Occ and non-occ [c]	Baseline	5 levels of PA: very low, low, moderate, high, very high	ER/PR, PostM	Adj [e]
Catsburg, 2014 [66] Canada	Canadian Study of Diet, Lifestyle and Health (CSDLH)	4,393 (1,094)	15	59 (mean)	PreM/PostM	Non-occ	Baseline	Hours per week and MET-hours per week	BMI, HRT, PreM/PostM	Adj
Brinton, 2014 [67] USA	National Institutes of Health-American Association of Retired Persons Diet and Health Study (NIH-AARP)	190,872 (7,384)	9	50-71	PostM	Occ and non-occ [c]	Baseline (past year)	Times per week (never/rarely,1-3/month, 1-2/wk, 3-4/wk, ≥5/wk)	PostM	Adj
Boeke, 2014 [68] USA	Nurses' Health Study II (NHS II)	75,669 (2,697)	14	25-42	PreM/PostM	Non-occ	Adolescence and adult (from age 12 to current age)	Total PA in MET-hours per week [b]	ER/PR [n], PreM/PostM	Nadj

PA: physical activity; Occ: occupational PA; Non-occ: non-occupational PA; NR: data not reported; MET: metabolic equivalent of task.

PostM: Post-menopausal women; PreM: Pre-menopausal women.

BMI: Body mass index; HRT: Hormone replacement therapy; ER: Estrogen receptor; PR: Progesterone receptor.

[a] Reported RR was adjusted for BMI: Adj: adjusted; Nadj: not adjusted; Adj/Nadj: both results were available (adjusted and not adjusted).

[b] These studies were not used for the dose-response analysis because RRs were reported for dichotomous exposure (Paffenbarger 1987) or only a high vs. low result was reported in the text (Rosenberg 2014 and Boeke 2014).

[c] Occupational and non-occupational PA were not distinguished.

[d] This study was only used for the stratified analysis on the type of PA as it used the same cohort as Breslow 2001 and reported data on occupational PA.

[e] RRs reported in the article were adjusted for BMI but as we recomputed RRs from cases and PYs we considered them as not adjusted for BMI in our analyses (see table S3).

First author, year Country	Study name	No. subjects (No. cancer cases)	Years of follow-up	Age of women	Menopausal status	Type of PA	Period in life for PA	Reporting of PA	Risk factor stratification	BMI adjusted [a]

[f] Data from the Swedish nationwide censuses in 1960 and 1970. We did not take the third cohort (women with the same job in 1960 and 1970) since it overlapped with the 1960 and 1970 censuses.

[g] "Whether all the women were cancer-free at the start of the follow-up was not evaluated".

[h] This study was only used for the stratified analysis on BMI and HRT use as this is the same cohort as Bardia 2006.

[i] Only RR for ER+/PR+ tumours was reported in this study.

[j] This study was only used for the stratified analysis on BMI as this is the same cohort as Phipps 2011.

[k] This study was only used for the stratified analyses on BMI and HRT use as this is the same cohort as Hildebrand 2013.

[l] This study was only used for the stratified analyses on hours/week, BMI and hormone receptor status as this is the same cohort as Boeke 2014. This study was also used for the dose-response analysis in MET-h/wk
instead of Boeke 2014.

[m] These studies used the same cohort as Brinton 2014, hence they were only used for the stratified analyses: Peters 2009 (october) for the analyses on hours/week and non-occupational PA; Peters 2009 (january) for the stratified analyses on BMI, HRT use and hormone receptor status; George 2010 for the occupational analysis.

[n] This study did not report ER/PR status but ER+ and ER- breast cancer. These stratified results were not used in our analyis.

[o] This study did not report ER/PR status but ER+ and triple negative breast cancer hence ER+ was considered as a proxy of ER+/PR+ and triple negative as a proxy of ER-/PR-.

[p] RR for occupational PA only was not reported.

[q] This study was only used for the stratified analysis on ER/PR status as the cohort was included in Margolis 2005.

Table 2: Physical activity and risk of breast cancer according to HRT use.

			Never users		Ever users		All women	
Study	**Year of start/end**	**Years of follow-up**	**No. Women (No. BC)**	**RR [95%CI]**	**No. Women (No. BC)**	**RR [95%CI]**	**No. Women (No. BC)**	**RR [95%CI]**
Moore, 2000 [35]	1986/1995	10	22,429 (-)	0.89 [0.74; 1.06]	13,934 (-)	0.94 [0.76; 1.16] a	37,105 (1,380)	0.95 [0.83; 1.10] b
Patel, 2003 [42]	1992/1997	5	35,013 (705)	0.64 [0.43; 0.95] c	35,247 (771)	0.87 [0.64; 1.19] cd	72,608 (1,520)	0.73 [0.51; 1.04] bc
Tehard, 2006 [50]	1990/2002	12	65,554 (1,189)	0.79 [0.67; 0.94] e	24,955 (1,095)	1.01 [0.85; 1.21]	90,509 (3,424)	0.90 [0.80; 1.02]
Howard, 2009 [55]	1994/2005	9	34,981 (139)	0.71 [0.43; 1.17]	10,650 (285)	1.15 [0.78; 1.70]	45,631 (864)	0.91 [0.74; 1.13]
Peters, 2009 [56]	1995/2003	7	100,757 (2,528) [f]	0.76 [0.67; 0.86]	82,105 (4,073) [f]	0.97 [0.88; 1.08]	182,862 (5,433) [f]	0.86 [0.79; 0.94] b
Catsburg, 2014 [66]	1995/2010	15	3,202 (724)	0.73 [0.55; 0.97]	1,215 (329)	0.83 [0.55; 1.26]	4,393 (1,094)	0.77 [0.61; 0.97]
SRR			261,936 (5,285)	0.78 [0.70; 0.87]	168,106 (6,553)	0.97 [0.88; 1.07]	433,105 (13,715)	0.88 [0.81; 0.95]

HRT: hormone replacement therapy; SRR: summary relative risk.

[a] RRs corresponding to past and current users were combined using a fixed-effect meta-analysis in order to get an ever users group.

[b] These results were not used in the main meta-analysis because these studies are duplicate with other studies.

[c] As the reference category was not the first one reported, the first two categories were merged and RRs were recomputed from cases and PY.

[d] Data from past and current users were taken into account to compute the RR for ever users.

[e] As RR for HRT non-users was not reported, it was computed from cases and PY.

[f] For the analysis on HRT use, both invasive and in-situ breast cancers were considered while for all women only invasive breast cancers were considered.

Table 3: Summary of studies that reported three or more categories of physical activity duration per day or per week.

First author, year of publication	Type of PA	Period of PA assessment	No. categories	% PYs in lowest PA category	% PYs in highest PA category	Lowest (h/w)	Highest (h/w)	RR highest vs. lowest	95% CI
Dirx, 2001 [37]	Total non-occupational	Baseline	4	22%	22%	<3.5	>10.5	0.76	0.58; 0.99
Chang, 2006 [47]	Vigorous non-occupational	Baseline	6	15%	21%	0	≥4	0.81	0.63; 1.05
Silvera, 2006 [49]	Vigorous non-occupational	Baseline (past one month)	4	28%	26%	0	>7	0.93	0.78; 1.10
Tehard, 2006 [50]	Vigorous non-occupational	Baseline	5 (3 after merging) [ab]	57%	13%	0 (inactive)	≥3	0.79	0.71; 0.89
Dallal, 2007 [51]	Vigorous non-occupational	Lifetime - between high school and current age	5	29%	11%	<0.5	>5	0.8	0.69; 0.94
Maruti, 2008 [53]	Vigorous non-occupational	Lifetime - adolescence and adult (from age 12 to current age)	5	21%	21%	<1	≥4	0.9	0.68; 1.18
Suzuki, 2008 [54]	Walking + exercise (occupational and non-occupational combined)	Baseline	3	NA	NA	NA	NA	0.76 c	0.58; 1.00
Howard, 2009 [55]	Vigorous activity (occupational and non-occupational combined)	Baseline (past year)	5 (4 after merging) [a]	50%	9%	0	≥4	0.82	0.63; 1.06
Peters, 2009 [57]	Moderate/vigorous non-occupational	Past 10 years	5	14%	24%	0 or rarely	>7	0.84	0.75; 0.94
Rosenberg, 2014 [22]	Vigorous non-occupational	Baseline (past year)	6 (5 after merging) [a]	53%	13%	<1	≥5	0.81	0.68; 0.98
Catsburg, 2014 [66]	Total non-occupational	Baseline	5	21% [d]	16% [d]	<1	>7.5	0.77	0.61; 0.97
Summary relative risk								**0.82**	**0.77;0.87**

PA: physical activity; PY: person-year; RR: relative risk; CI: confidence interval; NA: not available/applicable.

[a] Two first categories were merged as the reference category was not the first one reported.

[b] Two last categories were merged to get a category with at least 10% of subjects.

[c] RR computed using a fixed effect meta-analysis, see Table S3.

[d] % BC cases because PYs or No. of women in categories were not reported.

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Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies

Short title: Physical activity and breast cancer risk

Cécile Pizot [2], Mathieu Boniol [1,2], Patrick Mullie [2,3], Alice Koechlin [1,2], Magali Boniol [2], Peter Boyle [1,2] and Philippe Autier [1,2]

Figure captions

Figure 1. Flow chart of the literature search strategy to identify cohort studies on breast cancer risk and physical activity.

Figure 2. Forest plot of meta-analysis of breast cancer risk according to physical activity level in women. Individual studies are represented with their RR and 95% CI (highest versus lowest category of physical activity). The square size is proportional to the variance of the RR and the horizontal lines represent the corresponding 95% CI. Heterogeneity between studies was assessed through Q and I^2 statistics. Publication bias was evaluated using Begg, Egger and Macaskill tests.

Figure 3. Results from stratified analyses.

Figure 4. Dose-response relationship between breast cancer risk and physical activity in studies that measured physical activity in MET-h per week (A) or in hours per week (B).

A. MET-h/week

B. Hour/week

Figure 1

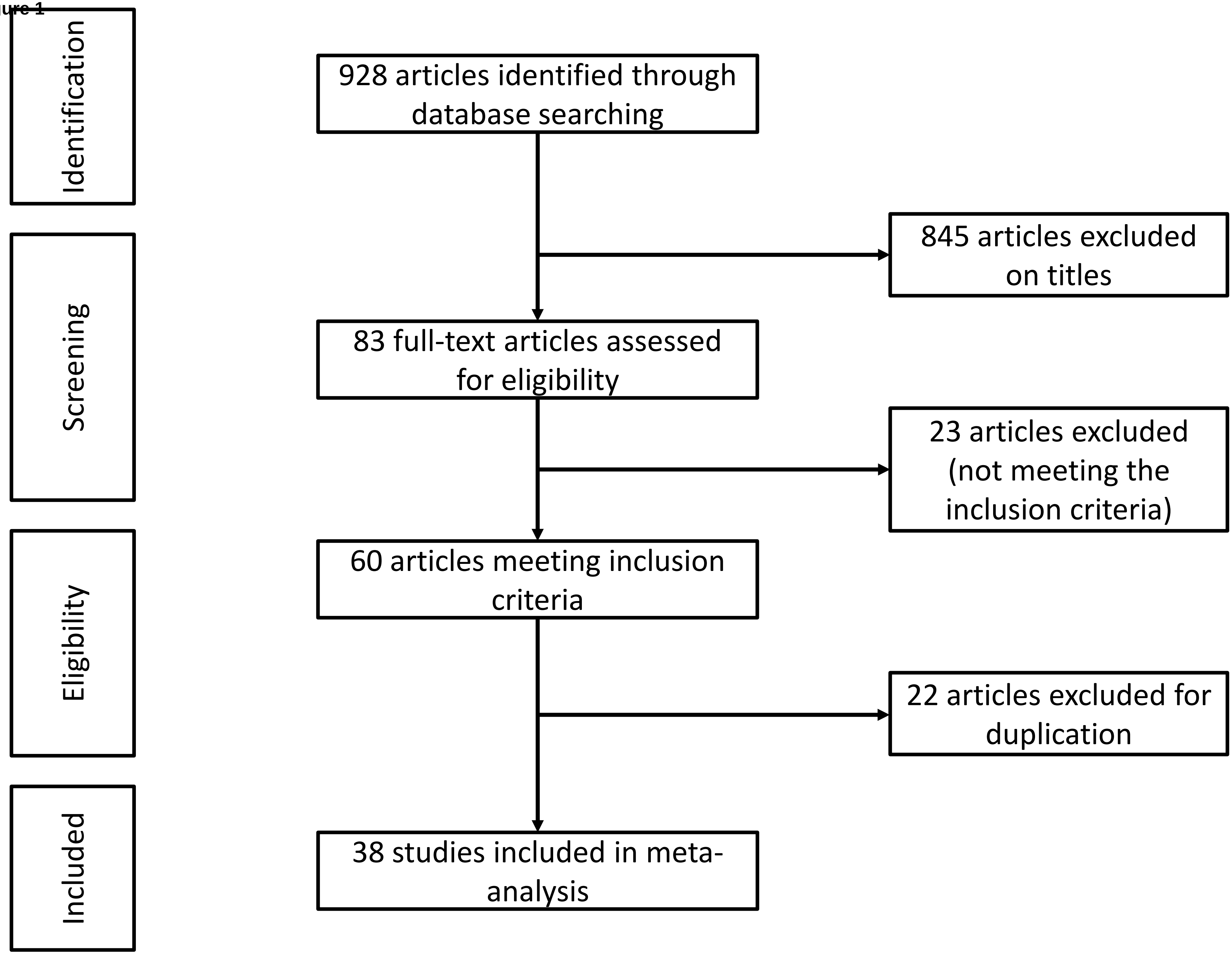
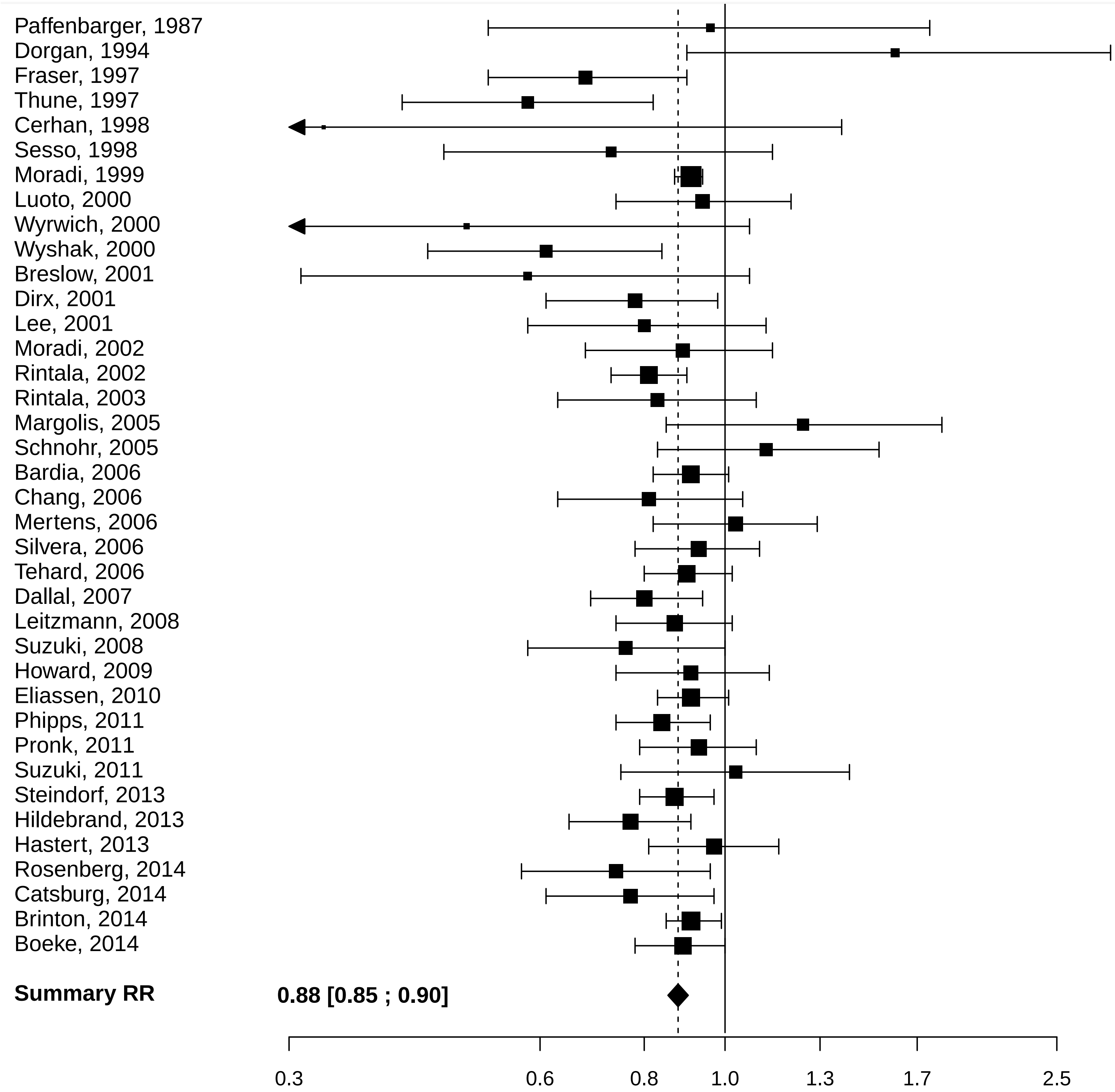

Identification
Screening
Eligibility
Included
928 articles identified through database searching
845 articles excluded on titles
83 full-text articles assessed for eligibility
23 articles excluded (not meeting the inclusion criteria)
60 articles meeting inclusion criteria
22 articles excluded for duplication
38 studies included in meta-analysis

Figure 2



I²: 29% [0 ; 53]

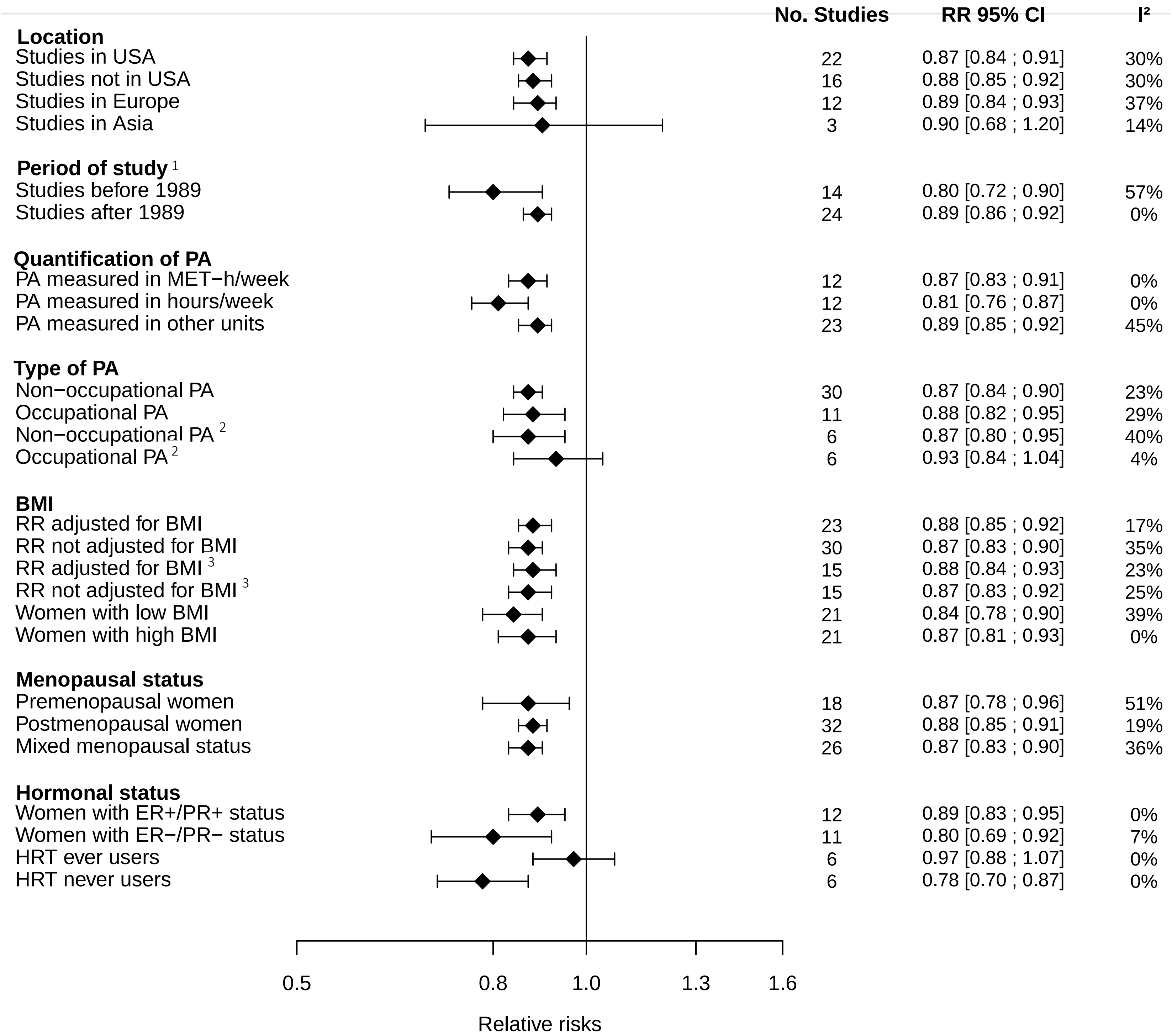
Q = 52.19; p = 0.05

Begg test: 0.05 ; p = 0.96

Egger test: −3.50 ; p < 0.01

Macaskill test: 1.30 ; p = 0.20

Figure 3

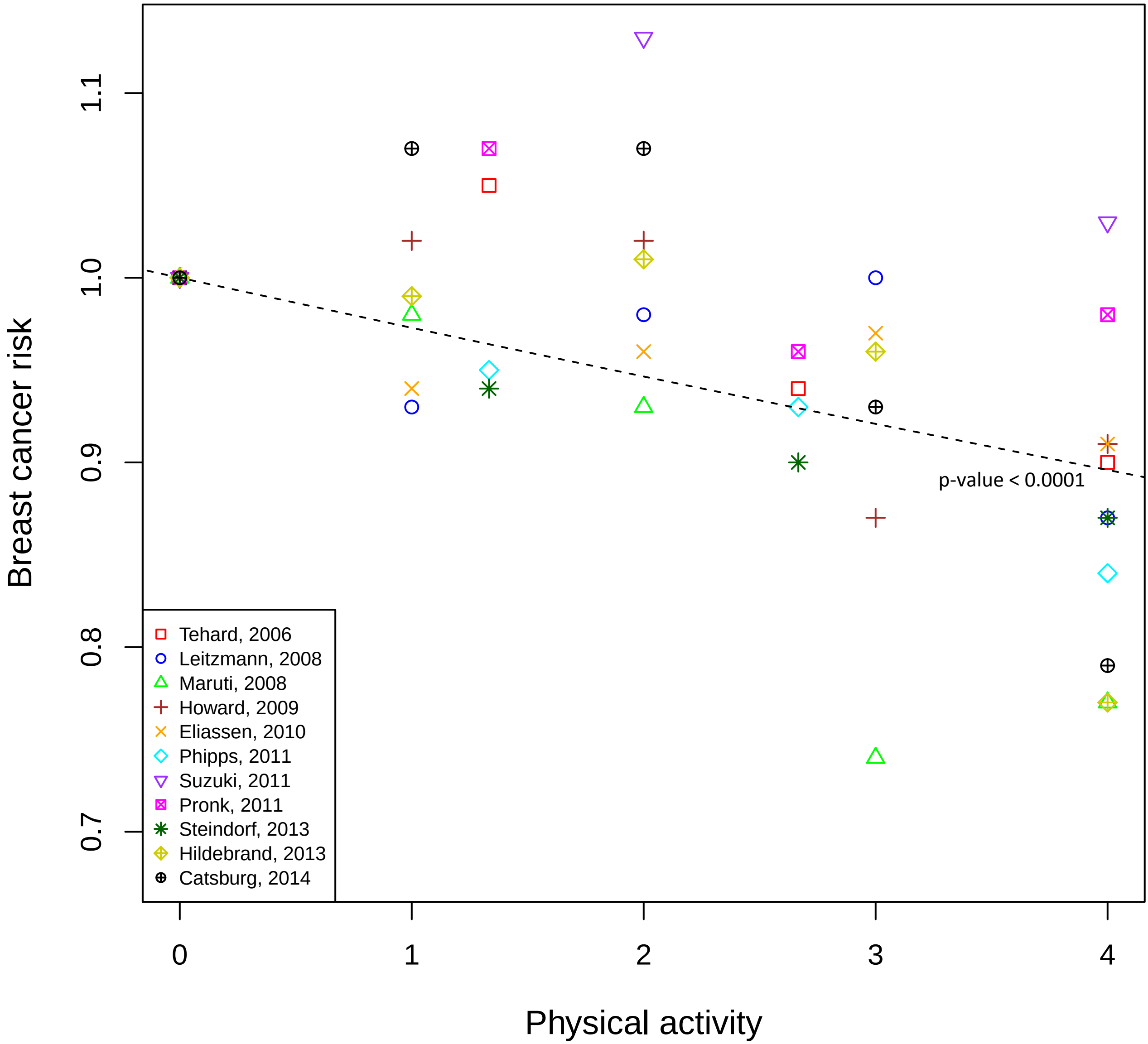


1 Mid-year of each cohort was taken into account

2 Including only studies which reported RRs for occupational PA and non-occupational PA seperately

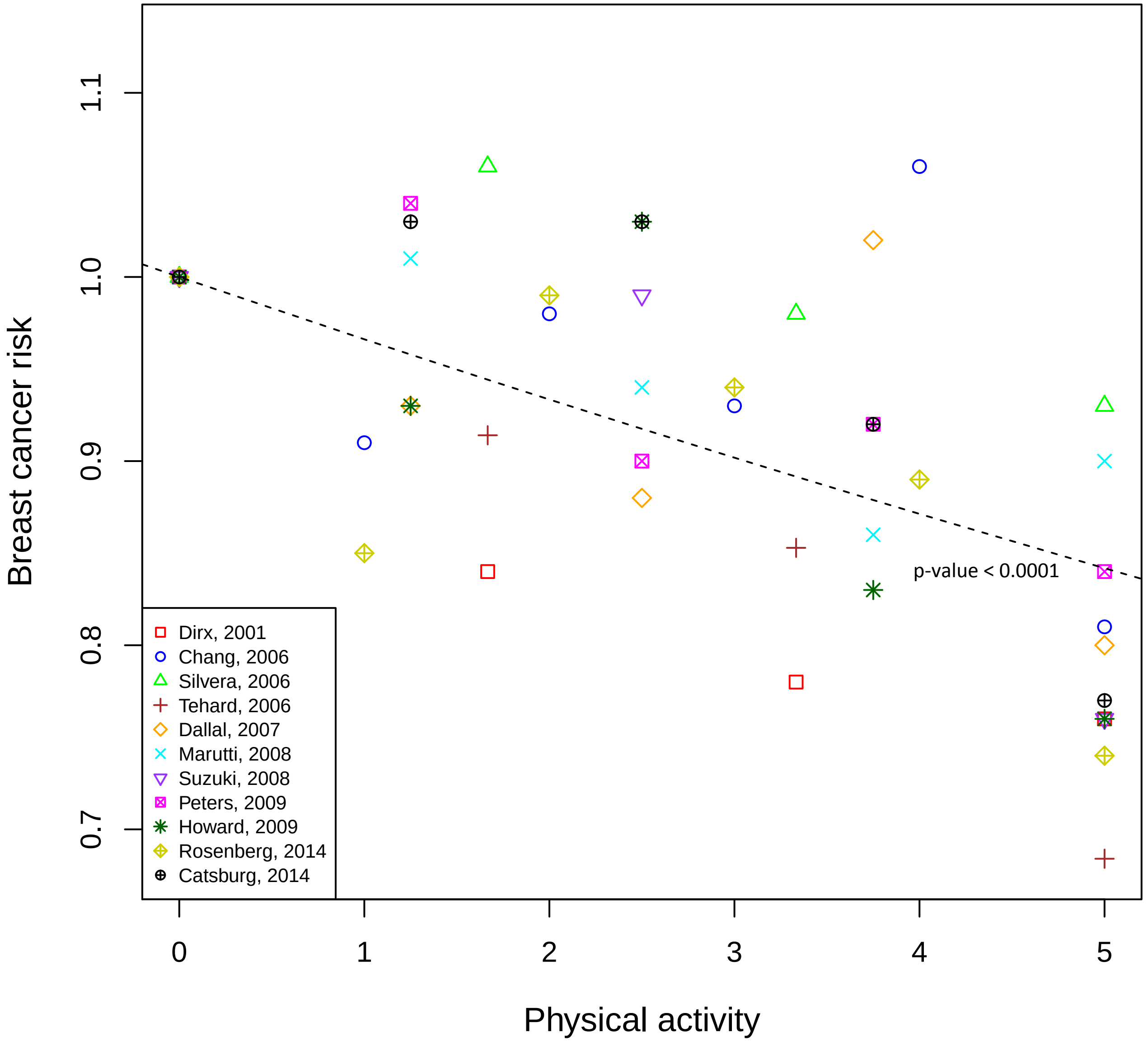
3 Including only studies which reported both RRs: adjusted for BMI and non-adjusted for BMI

Figure 4A



1.1
1.0
0.9
0.8
0.7
Breast cancer risk
0
1
2
3
4
Physical activity
p-value < 0.0001
Tehard, 2006
Leitzmann, 2008
Maruti, 2008
Howard, 2009
Eliassen, 2010
Phipps, 2011
Suzuki, 2011
Pronk, 2011
Steindorf, 2013
Hildebrand, 2013
Catsburg, 2014

Figure 4B



Breast cancer risk
1.1
1.0
0.9
0.8
0.7
p-value < 0.0001
Dirx, 2001
Chang, 2006
Silvera, 2006
Tehard, 2006
Dallal, 2007
Marutti, 2008
Suzuki, 2008
Peters, 2009
Howard, 2009
Rosenberg, 2014
Catsburg, 2014
0
1
2
3
4
5
Physical activity

***Conflict of Interest statement**

Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies

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Cécile Pizot [2], Mathieu Boniol [1,2], Patrick Mullie [2,3], Alice Koechlin [1,2], Magali Boniol [2], Peter Boyle [1,2] and Philippe Autier [1,2]

1. University of Strathclyde Institute of Global Public Health at iPRI, Allée Claude Debussy, Ecully (Lyon), France
2. International Prevention Research Institute, 95 cours Lafayette, 69006 Lyon, France
3. Faculty of Physical Education and Physiotherapy, Pleinstraat 2, 1050 Brussels, Belgium

Correspondence: Philippe Autier, University of Strathclyde Institute of Global Public Health at iPRI, Espace Européen, Building G, Allée Claude Debussy, 69130 Lyon Ouest Ecully, France; Email: philippe.autier@i-pri.org; Tel: +33 (0)4 72 17 11 99; Fax: +33(0)4 72 17 11 90.

Conflict of interest statement

None of the authors have any potential conflict of interest to declare in relation to the subject matter of this manuscript.

Online data supplements: Supplementary materials to the article:

Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies

Cécile Pizot [2], Mathieu Boniol [1,2], Patrick Mullie [2,3], Alice Koechlin [1,2], Magali Boniol [2], Peter Boyle [1,2] and Philippe Autier [1,2]

1. University of Strathclyde Institute of Global Public Health at iPRI, Allée Claude Debussy, Ecully (Lyon), France
2. International Prevention Research Institute, 95 cours Lafayette, 69006 Lyon, France
3. Faculty of Physical Education and Physiotherapy, Pleinstraat 2, 1050 Brussels, Belgium

Correspondence: Philippe Autier, University of Strathclyde Institute of Global Public Health at iPRI, Espace Européen, Building G, Allée Claude Debussy, 69130 Lyon Ouest Ecully, France; Email: philippe.autier@i-pri.org; Tel: +33 (0)4 72 17 11 99; Fax: +33(0)4 72 17 11 90.

Table S1 - Details on computation and data extraction

First author, year	Statistical computation and choice of data
Paffenbarger, 1987 [1]	RR was taken from table 3 for the main analysis. As there was no 95%CI, it was computed from cases and PY. This study was not used in the dose-response analysis in hours/week as RRs were reported for dichotomous exposure (<5h/wk vs. ≥5h/wk).
Dorgan, 1994 [2]	RR for the main analysis was taken from the full model of table 3.
Steenland, 1995 [3]	This study used the same cohort as Breslow 2001 [4], hence, it was not used for the main analysis but for the sub analysis on occupational activity as Breslow did not report this result. RR corresponding to occupational activity was taken from table 5. This RR was inverted since the reference category was a lot of physical activity instead of little physical activity.
Fraser, 1997 [5]	RR for the main analysis was taken from table 2. As the reported RR was for low vs. High physical activity, the RR was inverted to have a high vs. low result.
Thune, 1997 [6]	Only RRs based on the survey of 1977-1983 were taken in our analysis. For the main analysis, RRs from table 2 were used: RR corresponding to leisure time was combined with RR corresponding to work using a fixed-effect meta-analysis in order to get a global measure of physical activity. For the stratified analysis on menopausal status, RRs from table 3 were used and a combination of leisure time and work was performed. For the stratified analysis on BMI, RRs corresponding to leisure activity was taken from table 4 (BMI<22.8 and BMI>25.7).
Cerhan, 1998 [7]	RR for the main analysis was taken from the full model of table 4. As the reference category was not the first one, we merged the first two categories and re-computed the RR for each category (from cases and PY).
Sesso, 1998 [8]	RR for the main analysis was taken from table 2. For the stratified analysis on menopausal status (<55y and ≥55y) and BMI (<22 and ≥22), RRs were taken from table 3 and 4 respectively.
Moradi, 1999 [9]	For the main analysis, the most adjusted RR corresponding to the census of 1970 was taken from table 2. As the 95%CI was not really precise (only 2 digits were used), a new variance and 95%CI were computed from cases and PY reported in table 1 for the census of 1970. Then, the result was inverted as the reference category was high physical activity instead of low physical activity.
Luoto, 2000 [10]	The most adjusted RRs from table 2 were used for the main analysis: RRs corresponding to physical activity at leisure and to physical activity when commuting to work were combined using a fixed-effect meta-analysis in order to get a global non-occupational physical activity exposure. For the sub analyses on BMI (BMI<21 and BMI>26) and menopausal status (<50y and ≥50y), RRs from table 3 were used and as for the main analysis, RRs for leisure time and commuting to work were combined.
Wyrwich, 2000 [11]	For the main analysis, RR was taken from table 1. As the reference category was not the first one reported, we merged the first two categories and recomputed RR for the other categories. As the women were aged between 70-98y at baseline, they were considered as post-menopausal women.
Wyshak, 2000 [12]	For the main analysis, the most adjusted RR was taken from table 3.
Moore, 2000 [13]	This study used the same cohort as Bardia 2006 [14], hence, it was not used for the main analysis but for the sub analyses on BMI and HRT as Bardia did not report these results. RRs for the stratified analysis on BMI and on HRT use were taken from table 3. For the BMI, RRs corresponding to quartile 1 and 4 were taken into account. For HRT use, RRs corresponding to past and current users were combined using a fixed-effect meta-analysis in order to get an ever users group. As only post-menopausal women were included in the study, estrogen use was considered as HRT use.
Breslow et al. 2001 [4]	RRs for the main analysis and for the stratified analyses on menopausal status were taken from table 1. Menopausal status was defined with an age cutoff of 50y. Stratified analysis on BMI was performed on data from table 2 (including post-menopausal women only).
Dirx, 2001 [15]	RR for the main analysis was computed from total recreational activity (table 3) and energy expenditure from longest held job (occupational activity from table 4) using a fixed-effect meta-analysis in order to get a global measure of physical activity. For the sub analysis on h/week, only recreational activity result was used as occupational activity was expressed in kJ/min. For the sub analysis on BMI, data from table 6 and recreational activity were used (BMI<25 vs. BMI>30).
Lee, 2001 [16]	The most adjusted RRs from table 2 was taken for the main analysis, the post-menopausal analysis and ER+/PR+ analysis.

First author, year	Statistical computation and choice of data
Moradi, 2002 [17]	RRs reported in table 2 were taken for the main analysis: leisure time RR and occupation RR were combined using a fixed-effect meta-analysis in order to get a global measure of physical activity. For the stratified analysis on menopausal status, women born in 1901-1917 were considered post-menopausal and women born in 1918-1925 were considered pre-menopausal. RRs for the latter analysis were taken from table 2, leisure time RR and occupation RR were also combined. For the stratified analysis on BMI, RRs corresponding to leisure activity were taken from table 3: RRs for BMI at baseline (42-70y) in quartile I (BMI<22) and quartile IV (BMI>26.4) were used.
Rintale, 2002 [18]	For the main analysis, the most adjusted RRs were taken from table 2: as the results were stratified by age group, a fixed-effect meta-analysis was used to combine the three RRs (25-39y, 40-54y and ≥55y). For the pre-menopausal analysis, RRs from the age groups 25-39y and 40-54y were combined. For the post-menopausal analysis, the RR of the age group ≥55y was considered.
Mc Tiernan, 2003 [19]	This study used the same cohort as Phipps 2011 [20], hence, it was not used for the main analysis but for the sub analyses on BMI as Phipps did not report this result. RRs corresponding to BMI≤24.13 and BMI>28.44 were taken from table 3.
Patel, 2003 [21]	This study used the same cohort as Hildebrand 2013 [22], hence, it was not used for the main analysis but for the sub analyses on BMI and HRT as Hildebrand did not report these results. RRs were taken from table 5. As the reference category was not the first one reported, we merged the first two categories and recomputed RR for the other categories (from cases and PY). For the BMI analysis, RRs for BMI<25 and BMI≥30 were used. For the HRT analysis, RRs for current and former users were combined in order to create an ever users group comparable to the never users group.
Rintala, 2003 [23]	RR for the main analysis was taken from the abstract. For the stratified analysis on menopausal status, RRs from table 2 were used (pre-menopause :<50y and post-menopause: ≥50y).
Margolis, 2005 [24]	For the main analysis, the most adjusted RR corresponding to physical activity at enrollment was extracted from table 2. For the stratified analysis on menopausal status, RR were extracted from the text.
Schnohr, 2005 [25]	The most adjusted RR from table 2 was used for the main analysis.
Bardia, 2006 [14]	The most adjusted RR from table 2 was used for the main analysis and for the stratified analysis on hormone receptor status (ER+/PR+ and ER-/PR-).
Chang, 2006 [26]	The most adjusted RR from table 2 was used for the main analysis.
Mertens, 2006 [27]	The most adjusted RRs from table 3 were taken for the main analysis: RRs corresponding to leisure, work and sport were combined using a fixed-effect meta-analysis in order to get a global physical activity exposure. For the post-menopausal analysis, RRs were taken from table 4 and a combination of leisure, work and sport activity was also performed. For the occupational physical activity analysis, RR corresponding to work activity was taken from table 3. Concerning non-occupational physical activity, RRs for leisure and sport were taken from table 3 and were combined.
Silvera, 2006 [28]	For the main analysis, the most adjusted RR corresponding to vigorous physical activity (in min/day) was taken from table 2. RRs for pre-menopausal and post-menopausal women were taken from table 3. For the stratified analysis on BMI, RRs were computed from cases and PY (reported in table 5) for women with a BMI<25 and women with a BMI≥25.
Tehard, 2006 [29]	For the main analysis, the most adjusted RR corresponding to total physical activity was taken from table 3. For the stratified analysis on BMI, RR corresponding to BMI≥25 was taken from table 4. As RR for BMI<25 was not reported, it was computed form cases and PY. For the sub analysis on HRT use, RR for HRT users was taken from table 4. As RR for HRT non-users was not reported, it was computed from cases and PY. For the sub analysis on h/wk, RR corresponding to vigorous recreational activity was taken from table 3: the two first categories of PA were combined and RRs were recomputed using cases and PY as the two first categories of PA correspond to inactivity.
Dallal, 2007 [30]	In our main analysis, we took the most adjusted RR from table 2 corresponding to strenuous physical activity. For the stratified analysis on menopausal status (defined with a cutoff of 55y) and BMI (<25 vs. ≥25), we used data from table 4 based on lifetime strenuous physical activity. In the stratified analysis on ER/PR status, we used data from table 5 based on strenuous activity only (ER+/PR+ and ER-/PR-). For the stratified analysis with studies reporting physical activity in h/week, we only used the RR corresponding to strenuous lifetime activity from table 2.
Leitzmann, 2008 [31]	The most adjusted RR from table 2 was taken for the main analysis. For the sub analysis on BMI, RR corresponding to total physical activity was extracted from table 4 (BMI<25 and BMI≥25). For the sub analysis on hormone receptor status, RRs corresponding to ER+/PR+ and ER-/PR- were used. The latter RRs were based on vigorous physical activity and not total physical activity.

First author, year	Statistical computation and choice of data
Maruti, 2008 [32]	This study used the same cohort as Boeke 2014 [33], hence, it was not used for the main analysis but for the sub-analyses on hours/week, BMI, and hormone receptor status. For the hours/week analysis, RR corresponding to strenuous activity was extracted from table 2. For the sub analysis on BMI, RR was extracted from table 5 (BMI<25 and BMI≥25). For the sub analysis on hormone receptor status, results corresponding to ER+/PR+ and ER-/PR- were taken from the text. This study was also used for the dose-response analysis in MET-h/week instead of Boeke 2014 [33].
Suzuki, 2008 [34]	For the main analysis, the most adjusted RRs were taken from table 2: RR corresponding to time spent walking and RR corresponding to time spent exercising were combined using a fixed-effect meta-analysis in order to get a global physical activity exposure. The same RR was used for the sub analysis on hours/week. For the stratified analyses on menopausal status and BMI (<24 and ≥24), RRs were taken from table 5 (most active women compared to the rest of the women).
Howard, 2009 [35]	The most adjusted RR corresponding to total MET-score (from table 2) was taken for the main analysis. For the post-menopausal analysis, as the results were stratified on HRT use, RR for HRT ever users and RR for HRT never users were combined with a fixed-effect meta-analysis. For the sub analysis on hours/week, the most adjusted RR but without adjustment for other physical activities (to avoid colinearity) was taken from table 2.
Peters, 2009 [36]	This study used the same cohort as Brinton 2014 [37], hence, it was not used for the main analysis but for the sub-analyses on BMI, HRT and hormone receptor status. For the stratified analysis on hormone receptor status, RRs were taken from table 3 (ER+/PR+ vs. ER-/PR-). For the stratified analysis on HRT use (ever use vs. never use) and BMI (<25 vs ≥25), RRs were taken from table 4.
Peters, 2009 [38]	This study used the same cohort as Brinton 2014 [37], hence, it was not used for the main analysis but for the sub-analyses on the h/week and non-occupational activity. RR corresponding to the past 10y and to invasive breast cancers was taken from table 7.
George, 2010 [39]	This study used the same cohort as Brinton 2014 [37], hence, it was not used for the main analysis but for the sub-analysis on occupational activity. RR corresponding to occupational and household activity was taken from table 3.
Eliassen, 2010 [40]	For the main analysis, RR for baseline total physical activity was taken from table 2. For the stratified analysis on hormone receptor status, RRs for ER+/PR+ and ER-/PR- tumors were taken from the text.
Pronk, 2011 [41]	RRs for the main analysis came from table 2 (non-occupational activity) and 3 (occupational activity): the most adjusted RRs corresponding to all non-occupational activity and to cumulative energy expenditure were combined using a fixed-effect meta-analysis in order to get a global physical activity exposure. For the stratified analysis on menopausal status, RR for post-menopausal women was extracted from figure 1 whereas RR for pre-menopausal women was taken from the text (>8MET-h/wk vs. <8MET-h/wk). For the MET-h/week analysis, only non-occupational physical activity was taken into account as occupational activity was not reported in this unit. For the stratified analysis on BMI, RRs were taken from the text (BMI<23.73 vs. BMI≥23.73).
Phipps, 2011 [20]	This study was taken instead of McTiernan 2003 [19] for the main analysis as it was more recent. RRs from table 4 corresponding to total recreational physical activity were used. As the results were reported separately for ER+ and triple-negative breast cancers, we combined the both using a fixed-effect meta-analysis in order to get a global result. For the sub analysis on hormone receptor status, we used ER+ as a proxy of ER+/PR+ and triple-negative as a proxy of ER-/PR-. McTiernan 2003 [19] was only used for the sub analysis on BMI.
Suzuki, 2011 [42]	For the main analysis, the stratified analysis on menopausal status and the stratified analysis on hormone receptor status (ER+/PR+ and ER-/PR-), the most adjusted RRs corresponding to daily total physical activity were taken from table 3. For the sub analysis on non-occupational activity, the most adjusted RR corresponding to leisure-time activity was taken from table 2. For the stratified analysis on BMI, RRs corresponding to leisure-time activity were taken from table 4 (BMI<25 and BMI≥25).
Steindorf, 2013 [43]	For the main analysis, RR corresponding to total physical activity was taken from table 3. For the stratified analysis on menopausal status, RRs from table 3 were used (pre-menopause:≤50y and post-menopause: >50y). For the sub analysis on occupational activity, RR was taken from table 3. For the sub analysis on non-occupational activity and MET-h/week, RRs corresponding to combined recreational and household activities was taken from table 3. For the stratified analysis on hormone receptor status, RRs corresponding to total physical activity and to ER+/PR+ and ER-/PR- were taken from table 4. For the stratified analysis on BMI, RRs corresponding to total physical activity were taken from supplementary table S1 (normal: BMI<25) and S3 (obese: BMI>30).

First author, year	Statistical computation and choice of data
Hildebrand, 2013 [22]	This study was taken instead of Patel 2003 [21] for the main analysis as it was more recent. The most adjusted RR from table 2 corresponding to total recreational physical activity was taken for the main analysis. As the reference category was not the first one reported, we merged the first two categories and recomputed RR for the other categories. The study of Patel was kept for the sub analyses on BMI and HRT.
Hastert, 2013 [44]	For the main analysis, the most adjusted RR was taken from table 3. As this RR was adjusted for the body fatness recommendation, it was considered as adjusted for BMI.
Rosenberg, 2014 [45]	For the main analysis and for the stratified analysis on ER+/PR+ (ER+ was used as a proxy of ER+/PR+), RRs were taken from table 2. For the ER-/PR- sub-analysis, we considered triple negative breast cancer as a proxy of ER-/PR- and took the RR reported in the text. For the sub-analyses on BMI (<30 vs. ≥30) and menopausal status, RRs were taken from table 4. In the methods, it was said that all RRs were adjusted for BMI but in the footnotes of tables 2 and 4, RRs were not adjusted for BMI hence we considered that the RRs were not adjusted for BMI. For the sub-analysis on MET-h/wk, RR corresponding to vigorous exercise and brisk walking was taken from the text. Nevertheless, this study was not used in the dose-response analysis in MET-h/wk as only a high vs. low result was reported in this unit.
Borch, 2014 [46]	This study was based on a Norwegian cohort that was included in the study of Margolis 2005, hence, it was not used for the main analysis but for the stratified analysis on hormone receptor status (ER+/PR+ vs. ER-/PR-). RRs corresponding to PA at enrollment were taken from table 4. As the RRs were reported considering the intermediate category of PA as reference, we recomputed the RR using a basic cross product and assuming the first category of PA as reference. The variance and 95%CI were computed from cases and PY.
Catsburg, 2014 [47]	For the main analysis and for the stratified analysis on menopausal status, RRs corresponding to total hours per week were taken from table 3. For the sub-analyses on BMI (<25 vs. ≥25) and HRT use (never vs. ever), RRs corresponding to total hours per week were taken from supplementary tables 2 and 3 respectively. For the main analysis and all sub-analyses (except MET-h/wk analysis), we took into account the RRs corresponding to total hours per week as the total MET hours were computed from the hours/wk and CIs were smaller with hours/wk.
Brinton, 2014 [37]	For the main analysis, RR corresponding to physical activity in the past year was taken from table 2.
Boeke, 2014 [33]	For the main analysis, RR corresponding to lifetime physical activity was taken from the text. For the stratified analyses on menopausal status, RRs were taken from table 2. As the RRs were reported separately for each adolescent period, we combined all periods with a fixed-effect meta-analysis using the less adjusted RR (the most adjusted RR was adjusted for adult physical activity hence this result is prone to colinearity). This study was not used for the dose-response analysis in MET-h/wk as only a high vs. low result corresponding to lifetime physical activity was reported in the text. We preferably used Maruti 2008 [32]data for this dose-response analysis.

Table S2 - Duplicate studies that were excluded from main analysis

Study	Reason for exclusion
Frisch, 1987 [48]	Same cohort as Wyshak, 2000 [12].
Albanes, 1989 [49]	Same cohort as Breslow 2001 [4].
Vihko, 1992 [50]	Same cohort as Rintala, 2003 [23].
Pukkala, 1993 [51]	Same cohort as Rintala, 2003 [23].
Steenland, 1995 [3]	Same cohort as Breslow, 2001 [4]; Steenland, 1995 [3] was only used for the sub-analysis on occupational activity.
Byrne, 1996 [52]	Same cohort as Breslow, 2001 [4].
Rockhill, 1998 [53]	Same cohort as Boeke, 2014 [33].
Rockhill, 1999 [54]	Same cohort as Eliassen, 2010 [40].
Moore, 2000 [13]	Same cohort as Bardia, 2006 [14]; Moore, 2000 [13] was only used for the stratified analyses on BMI and HRT use.
McTiernan, 2003 [19]	Same cohort as Phipps, 2011 [20]; Mc Tiernan 2003 [19] was only used for the stratified analysis on BMI.
Colditz, 2003 [55]	Same cohort as Boeke, 2014 [33].
Patel, 2003 [21]	Same cohort as Hildebrand 2013 [22]; Patel 2003[21] was only used for the stratified analyses on BMI and HRT use.
Lahmann, 2007 [56]	Same cohort as Steindorf 2013 [43].
Ji, 2008 [57]	Same cohort as Pronk 2011 [41].
Inoue, 2008 [58]	Same cohort as Suzuki 2011 [42].
Maruti, 2008 [32]	Same cohort as Boeke 2014 [33]; Maruti 2008 [32] was only used for the stratified analyses on hours/week, BMI, and hormone receptor status.
Peters, 2009 [38]	Same cohort as Brinton 2014 [37]; Peters 2009 [38] was only used for the stratified analyses on hours/week and non-occupational physical activity.
Peters, 2009 [36]	Same cohort as Brinton 2014 [37]; Peters 2009 [36] was only used for the stratified analyses on BMI, hormone receptor status and HRT use.
George, 2010 [39]	Same cohort as Brinton 2014 [37]; Peters 2009 [38] was only used for the stratified analysis on occupational physical activity.
Fournier, 2014 [59]	Same cohort as Tehard 2006 [29]; they used recent physical activity (previous four years) instead of baseline physical activity which might imply reverse causation.
McKenzie, 2014 [60]	Same cohort as Steindorf 2013 [43] but they used a smaller sample size and smaller follow-up. Moreover, they focused on healthy lifestyle index and not precisely on physical activity.
Borch, 2014 [46]	This study was based on a Norwegian cohort that was included in the study of Margolis 2005 [24], hence, it was only used for the stratified analysis on hormone receptor status.

Table S3 - Breast cancer types included in prospective studies

First author, year	Type of cancer considered in results	Invasive only [a]
Paffenbarger, 1987 [1]	No information about the type of breast cancer (invasive or in-situ or both).	N
Dorgan, 1994 [2]	No information about the type of breast cancer (invasive or in-situ or both).	N
Steenland, 1995 [3]	No information about the type of breast cancer (invasive or in-situ or both).	N
Fraser, 1997 [5]	RRs reported for invasive breast cancer only.	Y
Thune, 1997 [6]	RRs reported for invasive breast cancer only.	Y
Cerhan, 1998 [7]	RR reported for all, localized, and regional/disseminated breast cancers. We only used the result for all cancers.	Y
Sesso, 1998 [8]	No information about the type of breast cancer (invasive or in-situ or both).	N
Moradi, 1999 [9]	RRs reported for invasive breast cancer only.	Y
Luoto, 2000 [10]	No information about the type of breast cancer (invasive or in-situ or both).	N
Wyrwich, 2000 [11]	RR reported for all, localized, and regional/distant breast cancers. We only used the result for all cancers.	Y
Wyshak, 2000 [12]	No information about the type of breast cancer (invasive or in-situ or both).	N
Moore, 2000 [13]	No information about the type of breast cancer (invasive or in-situ or both) but Bardia 2006 [14] used the same cohort and included both invasive and in-situ breast cancers.	N
Breslow, 2001 [4]	No information about the type of breast cancer (invasive or in-situ or both).	N
Dirx, 2001 [15]	Results on invasive breast cancers only as the in-situ breast cancers were excluded from the study.	Y
Lee, 2001 [16]	322 invasive and 79 in-situ breast cancers were included in this study. Results were reported for all cancers only.	N
Moradi, 2002 [17]	No information about the type of breast cancer (invasive or in-situ or both).	N
Rintala, 2002 [18]	No information about the type of breast cancer (invasive or in-situ or both).	N
McTiernan, 2003 [19]	This study included 85% of invasive breast cancers and 15% of in-situ breast cancers. Reported RRs were for all cancers combined.	N
Patel, 2003 [21]	This study included in-situ, localized and regional/distant breast cancers but for the sub analyses on BMI and HRT only RRs for all cancers were reported.	Y
Rintala, 2003 [23]	No information about the type of breast cancer (invasive or in-situ or both).	N
Margolis, 2005 [24]	RRs reported for invasive breast cancers only.	Y
Schnohr, 2005 [25]	No information about the type of breast cancer (invasive or in-situ or both).	N

First author, year	Type of cancer considered in results	Invasive only [a]
Bardia, 2006 [14]	Results reported for both invasive and in-situ breast cancers combined.	N
Chang, 2006 [26]	Results reported on all cases but there were 13% of in-situ breast cancers and 27% of non-confirmed breast cancers. Authors said that the results with the exclusion of in-situ and non-confirmed cases did not differ from the results for all cases.	N
Mertens, 2006 [27]	No information about the type of breast cancer (invasive or in-situ or both).	N
Silvera, 2006 [28]	No information about the type of breast cancer (invasive or in-situ or both).	N
Tehard, 2006 [29]	RRs reported for invasive breast cancers only as in-situ breast cancers were excluded.	Y
Dallal, 2007 [30]	2,649 invasive breast cancers and 593 in-situ breast cancers included in the study but results were reported separately for invasive and in-situ breast cancers. We only took invasive breast cancer results in our analyses.	Y
Leitzmann, 2008 [31]	This study included 17% of in-situ breast cancers and reported RRs for all cancers as the results remained the same when in-situ breast cancers were excluded.	N
Maruti, 2008 [32]	RRs reported for invasive breast cancers only as in-situ and unconfirmed breast cancers were excluded.	Y
Suzuki, 2008 [34]	No information about the type of breast cancer (invasive or in-situ or both).	N
Howard, 2009 [35]	RRs reported for invasive breast cancers only as in-situ breast cancers were excluded.	Y
Peters, 2009 [36]	5,433 invasive breast cancers and 1176 in-situ breast cancers included in the study but results were reported separately for both type of cancers. For the stratification on hormone receptor status only RRs for invasive breast cancers were reported. Nevertheless, for the sub analyses on BMI and HRT use, RRs were reported for all breast cancers.	N
Peters, 2009 [38]	3,522 invasive breast cancers and 736 in-situ breast cancers included in the analysis but results were reported separately for both type of cancers. We only considered the results for invasive breast cancers in our analyses.	Y
George, 2010 [39]	2,866 invasive breast cancers and 570 in-situ breast cancers but results were reported separately for both type of cancers.	Y
Eliassen, 2010 [40]	RRs reported for invasive breast cancers only.	Y
Pronk, 2011 [41]	RRs reported for invasive breast cancers only.	Y
Phipps, 2011 [20]	RRs reported for invasive breast cancers only as in-situ breast cancers were censored.	Y
Suzuki, 2011 [42]	No information about the type of breast cancer (invasive or in-situ or both).	N
Steindorf, 2013 [43]	RRs reported for invasive breast cancers only.	Y
Hildebrand, 2013 [22]	No information about the type of breast cancer (invasive or in-situ or both) but Patel 2003 [21]used the same cohort and included invasive breast cancers defined as localized and regional/distant breast cancers.	N
Hastert, 2013 [44]	RRs reported for invasive breast cancers only as in-situ breast cancers were censored.	Y
Rosenberg, 2014 [45]	RRs reported for invasive breast cancers only as in-situ breast cancers were censored.	Y

First author, year	Type of cancer considered in results	Invasive only [a]
Borch, 2014 [46]	RRs reported for invasive breast cancers only.	Y
Catsburg, 2014 [47]	RRs reported for invasive breast cancers only.	Y
Brinton, 2014 [37]	RRs reported for invasive breast cancers only as in-situ breast cancers were censored.	Y
Boeke, 2014 [33]	RRs were reported for both types of breast cancer as results were similar for invasive and in situ cases.	N

[a] Y/N: Yes/No

Table S4 - Assessment of physical activity in prospective studies (duplicate studies from which some data were used are in light grey)

Study	Type of PA	Units used				Categories		Period in life for PA assessment		
	Occupational/non-occupational/both Total/Vigorous	MET-h/ week [a]	Hours/ week [b]	KJ/d (energy per unit of time)	Other	3+ categories	2 categories	Baseline [c]	During lifetime	During follow-up (FU)
Paffenbarger, 1987 [1]	Non-occupational		y				y		Early college	
Dorgan, 1994 [2]	Both PA combined				y	y		y		
Steenland, 1995 [3]	Occupational				y	y		y		
Fraser, 1997 [5]	Both PA combined				y	y		y		
Thune, 1997 [6]	Non-occupational				y	y		y		
Thune, 1997 [6]	Occupational				y	y		y		
Cerhan, 1998 [7]	Non-occupational				y	y		y		
Sesso, 1998 [8]	Non-occupational			y		y		y		
Moradi, 1999 [9]	Occupational				y	y			Adult life (1960 and 1970 censuses)	
Luoto, 2000 [10]	Non-occupational				y	y		y		
Wyrwich, 2000 [11]	Non-occupational				y	y		y		
Wyshak, 2000 [12]	Non-occupational				y		y		College	
Moore, 2000 [13]	Non-occupational				y	y		y		
Breslow, 2001 [4]	Non-occupational				y	y			Long term (baseline + 10y before)	
Dirx, 2001 [15]	Non-occupational - total PA		y			y		y		
Dirx, 2001 [15]	Occupational			y		y			y	
Lee, 2001 [16]	Non-occupational			y		y		y		
Moradi, 2002 [17]	Non-occupational				y	y			Adult (25-50 years)	

Study	Type of PA	Units used				Categories		Period in life for PA assessment		
	Occupational/non-occupational/both Total/Vigorous	MET-h/ week [a]	Hours/ week [b]	KJ/d (energy per unit of time)	Other	3+ categories	2 categories	Baseline [c]	During lifetime	During follow-up (FU)
Moradi, 2002 [17]	Occupational				y	y				
Rintala, 2002 [18]	Occupational				y	y			Baseline, at age 20 and at age 35	
McTiernan, 2003 [19]	Non-occupational	y				y		y		
Patel, 2003 [21]	Non-occupational	y				y		y		
Rintala, 2003 [23]	Occupational				y		y		y	
Margolis, 2005 [24]	Non-occupational				y	y		y		
Schnohr, 2005 [25]	Non-occupational				y	y		y		
Bardia, 2006 [14]	Non-occupational				y	y		y		
Chang, 2006 [26]	Non-occupational - vigorous PA		y			y		y		
Mertens, 2006 [27]	Non-occupational				y	y		y		
Mertens, 2006 [27]	Occupational				y	y		y		
Silvera, 2006 [28]	Non-occupational - vigorous PA		y			y		y		
Tehard, 2006 [29]	Non-occupational - total PA	y				y		y		
Tehard, 2006 [29]	Non-occupational - vigorous PA		y			y		y		
Dallal, 2007 [30]	Non-occupational - strenuous PA		y			y			Between high school and curent age	
Leitzmann, 2008 [31]	Both PA combined - total PA	y				y		y		
Maruti, 2008 [32]	Non-occupational - total PA	y				y			Adolescence and adult (from age 12 to current age)	

Study	Type of PA	Units used				Categories		Period in life for PA assessment		
	Occupational/non-occupational/both Total/Vigorous	**MET-h/ week [a]**	**Hours/ week [b]**	**KJ/d (energy per unit of time)**	**Other**	**3+ categories**	**2 categories**	**Baseline [c]**	**During lifetime**	**During follow-up (FU)**
Maruti, 2008 [32]	Non-occupational - strenuous PA		y			y			Adolescence and adult (from age 12 to current age)	
Suzuki, 2008 [34]	Both PA combined		y			y		y		
Howard, 2009 [35]	Both PA combined - total PA	y				y		y		
Howard, 2009 [35]	Both PA combined - strenuous PA		y			y		y		
Peters, 2009 [36]	Both PA combined				y	y		y		
Peters, 2009 [38]	Non-occupational - moderate/vigorous PA		y			y			Past 10y	
George, 2010 [39]	Occupational				y	y		y		
Eliassen, 2010 [40]	Non-occupational	y				y				Baseline (past year) + updtate every 2 or 4 years
Pronk, 2011 [41]	Non-occupational - total PA	y				y			Baseline + 5 years before interview	
Pronk, 2011 [41]	Occupational			y		y			y	
Phipps, 2011 [20]	Non-occupational - total PA	y				y		y		
Suzuki, 2011 [42]	Non-occupational				y	y				Baseline + update 5 years after
Suzuki, 2011 [42]	Both PA combined - total PA	y				y				
Steindorf, 2013 [43]	Non-occupational	y				y		y		
Steindorf, 2013 [43]	Occupational				y	y		y		
Steindorf, 2013 [43]	Both - total PA				y			y		

Study	Type of PA	Units used				Categories		Period in life for PA assessment		
	Occupational/non-occupational/both Total/Vigorous	**MET-h/ week [a]**	**Hours/ week [b]**	**KJ/d (energy per unit of time)**	**Other**	**3+ categories**	**2 categories**	**Baseline [c]**	**During lifetime**	**During follow-up (FU)**
Hildebrand, 2013 [22]	Non-occupational - total PA	y				y				Baseline + updated 3 times during FU
Hastert, 2013 [44]	Non-occupational				y		y		Past 10y	
Rosenberg, 2014 [45]	Non-occupational - vigorous PA		y			y		y		
Borch, 2014 [46]	Both PA combined				y	y		y		
Catsburg, 2014 [47]	Non-occupational - total PA	y	y			y		y		
Brinton, 2014 [37]	Both PA combined				y	y		y		
Boeke, 2014 [33]	Non-occupational - total PA	y				y			Adolescence and adult (from age 12 to current age)	

[a] 14 articles reported MET-h/week but 11 were not duplicate studies.

[b] 12 articles reported hours/week but 11 classified in 3 categories or more.

[c] Usually, physical activity during the year preceding cohort inception.

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