Published in final edited form as:

Breast Cancer Res Treat. 2012 September ; 135(2): 367–380. doi:10.1007/s10549-012-2152-z.

Physical activity and mammographic breast density: a systematic review

Lusine Yaghjian,

Department of Surgery, Division of Public Health Sciences, Washington University in St. Louis School of Medicine, 660 S. Euclid Avenue, Campus Box 8100, St. Louis 63110, MO, USA

Graham A. Colditz, and

Department of Surgery, Division of Public Health Sciences, Washington University in St. Louis School of Medicine, 660 S. Euclid Avenue, Campus Box 8100, St. Louis 63110, MO, USA. Institute for Public Health, Washington University in St. Louis, St. Louis, MO, USA. Alvin J Siteman Cancer Center, St. Louis, MO, USA

Kathleen Wolin

Department of Surgery, Division of Public Health Sciences, Washington University in St. Louis School of Medicine, 660 S. Euclid Avenue, Campus Box 8100, St. Louis 63110, MO, USA. Institute for Public Health, Washington University in St. Louis, St. Louis, MO, USA. Alvin J Siteman Cancer Center, St. Louis, MO, USA

Lusine Yaghjian: yaghjianl@wudosis.wustl.edu; Graham A. Colditz: colditzg@wudosis.wustl.edu; Kathleen Wolin: wolink@wustl.edu

Abstract

Studies show a protective relationship between physical activity and breast cancer risk across the life course from menarche to postmenopausal years. Mammographic breast density is a known and strong breast cancer risk factor. Whether the association of physical activity with breast cancer risk is mediated through mammographic breast density is poorly understood. This systematic review summarizes published studies that investigated the association between physical activity and mammographic breast density and discusses the methodological issues that need to be addressed. We included in this review studies that were published before October 31, 2011 that were accessible in full-text format and were published in English. We identified 20 studies through the PubMed Central, BioMed Central, Embase, and Scopus and using the search terms “physical activity and breast density” and “exercise and breast density” as well as through manual searches of the bibliographies of the articles identified in electronic searches. We found no evidence of association between physical activity and breast density across the studies by grouping them first by the timing of physical activity assessment (in adolescence, current/recent, past, and lifetime) and then by women’s menopausal status (premenopausal and postmenopausal). Given the strength of the relationship between physical activity and breast cancer and the null findings of this review, it is unlikely that the effect of physical activity is mediated through an effect on breast density.

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Correspondence to: Lusine Yaghjian, yaghjianl@wudosis.wustl.edu.

Electronic supplementary material The online version of this article (doi:10.1007/s10549-012-2152-z) contains supplementary material, which is available to authorized users.

Conflict of interest The authors declare that they have no competing interests.

Keywords

Breast density; Physical activity; Exercise; Breast cancer risk

Introduction

Mammographic breast density is a well-established and very strong predictor of breast cancer risk [1–4]. Appearance of the breast on the mammogram is a reflection of the amount of fat, connective, and epithelial tissue in the breast [3]. Light (non-radiolucent) areas on the mammogram represent the fibrous and glandular tissues (“mammographically dense”) and the dark (radiolucent) areas are primarily fat. Women with 75 % or greater percent density (proportion of the breast that appears dense on the mammogram out of the total breast area) are at four to six times greater risk of breast cancer compared with women with fatty breasts [3, 5–7]. Breast density is not a static characteristic and changes over time [8]. Use of postmenopausal hormones, especially combined estrogen plus progestin therapy, increases breast density as early as after 3–6 months of hormone use [9–11]. However, this increase is reversible [12]. Breast density decreases with age, especially during the menopausal transition and during tamoxifen use [13–15].

In 2007, the World Cancer Research Fund and the American Institute for Cancer Research concluded that high levels of physical activity protect against postmenopausal breast cancer [16]. A recent systematic review of 33 cohort studies and 40 case–control studies reported a lower breast cancer risk in women with highest versus lowest levels of physical activity in 40 % of the studies [17]. Null results were reported in 26 % of the studies, 30 % reported either borderline or not statistically significant breast cancer risk reduction, and 4 % reported a non-statistically significant positive association of physical activity with breast cancer risk [17]. Reduction in breast cancer risk across case–control studies was greater than in cohort studies (30 vs. 20 %) [17]. Physical activity at any age throughout life reduces breast cancer risk, but the strongest reduction was seen for physical activity after age 50 (average risk reduction of 17 %) followed by activity in adolescence (average risk reduction of 16 %), middle adulthood (30s/40s, average risk reduction of 15 %), and early adulthood (20s, average risk reduction of 8 %) [17]. A greater risk reduction was reported for recreational and household activity, followed by walking/cycling and occupational activity as well as for vigorous level and longer duration of physical activity [17]. An inverse association between physical activity and the risk of breast cancer was reported in both pre- and postmenopausal women; the average reduction in breast cancer risk, however, was greater in postmenopausal than in premenopausal women (31 vs. 27 %) [17]. A greater risk reduction was seen in lean women as compared to women with Body Mass Index (BMI) ≥ 22 kg/m², in women without a family history of breast cancer as compared to women with a family history, and in parous women as compared to nulliparous women [17].

Several biologic mechanisms have been suggested to explain the inverse association of physical activity with breast cancer risk. Among those mechanisms are decreased body fat, decreased production of steroid hormones and as a result, reduced cumulative exposure to endogenous reproductive hormones, changes in the menstrual cycle frequency and duration, improved insulin sensitivity, reduced adipokine levels, and decreased inflammation [17, 18].

Whether the association of physical activity with breast cancer risk is mediated through mammographic breast density remains unclear. The purpose of this review is to summarize published studies on the association between physical activity and mammographic breast density and to identify the methodological issues that need to be addressed in future studies.

Literature search

Published studies were identified using the PubMed Central (U.S. National Institutes of Health [NIH]), BioMed Central, Embase, and Scopus literature search (through Washington University in St. Louis). We included in this review studies published before October 31, 2011 that were accessible in full-text format and were published in English. Articles were searched using the combination of the terms “physical activity and breast density” and “exercise and breast density.” Bibliographies of the articles identified in the electronic searches were then searched manually for additional relevant references. From this review, we excluded the studies that did not show their findings on the association between physical activity and breast density.

From each identified article, we abstracted the data on study design, sample size, physical activity (timing, type, dose, and intensity), characteristics of the study population (premenopausal, postmenopausal, and race/ethnicity), breast density assessment method and timing of the mammogram, and results. Even though some of the studies that sampled their participants cross-sectionally asked them to recall physical activity earlier in life, those studies are considered as cross-sectional in design for the purpose of this review.

Statistical analysis

We compared the results across the studies by grouping them first by the timing of physical activity assessment (in adolescence, current/recent [within 5 years preceding the mammogram], past [>5 years before the mammogram], and lifetime [from childhood through adulthood]) and then by women's menopausal status (premenopausal and postmenopausal). In the statistical comparisons, we excluded studies by Lopez et al. [19] (investigation of association between inactivity and breast density), Sala et al. [20] (timing of the physical activity assessment not specified), and Marmara et al. [21] (reported ORs values <0 and 95 % CIs sometimes not centered around the point estimate). These studies, however, were included in the qualitative review. In a secondary analysis, we also excluded two studies in breast cancer survivors.

Variability of the studies with respect to the study populations, type, dose and timing of physical activity, density estimation, and presentation of the results makes a direct comparison across the studies difficult. For these reasons, we were unable to conduct a formal meta-analysis across the studies. Instead, the Mann–Whitney–Wilcoxon rank-sum test was used to combine the results of the studies by the timing of physical activity, overall and by menopausal status [22]. For the studies that did not report the overall findings, but rather presented them stratified by either menopausal status or other characteristics (BMI, age at physical activity, etc.), we extrapolated the overall findings by calculating the average for adjusted mean percent density weighted by the number of participants. Significance of the test was assessed at the $\alpha = 0.05$ significance level. All analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC).

Results

Our search yielded 1,884 manuscripts, from which we identified 20 eligible studies (Fig. 1). Key characteristics of these studies are summarized in Table 1. The earliest study we found was published in 1999. The majority of the published studies originated in the United States (60 %). Most of the studies sampled their participants cross-sectionally (75 %). Three studies were longitudinal and one study utilized a case–control design. All studies, except two whose populations were composed of survivors, investigated the associations in healthy (breast cancer–free) women.

Majority of the studies (65 %) had a large sample size (>500 participants): The mean number of participants was 887 (median 675, range 95–2,720) with the total number of 5,345 pre- or peri- and 11,324 postmenopausal women across all 20 studies. Most of the studies included both pre- and postmenopausal women in their study population (16 or 80 %), two studies had only postmenopausal participants, and one study included only pre-menopausal women. Among studies with mixed population with respect to menopausal status, seven (44 %) reported the results separately for pre- and postmenopausal women.

Most studies (14 or 70 %) assessed the physical activity level at the time of the mammogram or within the 5 years before the mammogram date; four studies assessed physical activity within more than 5 years preceding the mammogram. Five studies investigated the association of physical activity level during adolescence (between 7 and 20 years of age) and adult breast density and two studies investigated the associations of lifetime physical activity with breast density. The majority of the studies (50 %) assessed non-occupational physical activity only, while others (30 %) assessed physical activity across multiple domains (recreational, household/caregiving, and occupational). Nine studies (45 %) used the metabolic equivalent (MET) to assess the intensity of physical activity, by calculating an index or a score incorporated in the analyses.

The majority of the studies (14 or 70 %) included predominantly white women. Two studies included only Hispanic women, one study included only Asian women, and two other studies had a mixed population with respect to race/ethnicity. Most of the studies (65 %) quantified percent breast density (proportion of dense breast tissue out of the total breast area) using computerized techniques. Of those, eight studies also measured the absolute dense area. Seven of the studies assessed breast density qualitatively using one of the existing breast density classification systems (Wolfe's density categories, Tabar's classification, six-category [Boyd] classification, or BI-RADS breast density classification). The absolute difference between adjusted mean percent breast density at the extremes of physical activity in different subpopulations across seven studies (Fig. 2) varied between 0.1 and 10.7 %. Among the studies that reported their findings as ORs, the change in risk for denser density pattern in women with the highest physical activity level versus the lowest level varied between 15 % reduction and 17 % increase, depending on the study subpopulation. Among the studies that reported their findings as regression coefficient estimates, beta varied between –2.62 and 3.18.

In Table 2, we present for each study the characteristics of the study population as well as details of physical activity assessment and breast density estimation approach (see Table 2). In the following, we summarize findings of the studies on the association between physical activity/inactivity and mammographic breast density by the timing of physical activity and by menopausal status as presented in Supplementary Tables S1–S6.

Physical activity in adolescence and adult breast density

Five studies investigated the association between adult breast density and adolescent physical activity (between age 7 and 20 years) (Fig. 3; Table 2). When we combined data across five studies (Table 3), we observed no statistically significant differences in breast density at the extreme levels of physical activity ($p = 0.6$). Similarly, no statistically significant differences were observed in either pre- or post-menopausal women across three studies that reported the results separately by menopausal status ($p = 1.0$ in pre-menopausal women; $p = 0.6$ in postmenopausal women).

Past physical activity (>5 years before the mammogram) and breast density

Four studies investigated the association of past physical activity and breast density (Fig. 4; Table 2). We found no statistically significant differences in breast density at the extreme levels of physical activity ($p = 1.0$) when we combined data across four studies (Table 3). No statistically significant differences were observed in a stratified analysis by menopausal status ($p = 1.0$ in premenopausal women; $p = 0.2$ in postmenopausal women).

Recent physical activity (within 5 years before the mammogram) and breast density

Fourteen studies investigated the association of recent physical activity/inactivity (within 5 years before mammogram) with breast density (Fig. 5; Table 2). No statistically significant differences in breast density at the extreme levels of physical activity ($p = 0.6$) were observed when data across 12 studies (excluding Lopez et al. and Marmara et al.) were combined (Table 3). No statistically significant differences were observed in either pre- or postmenopausal women across the studies ($p = 0.1$ in premenopausal women; $p = 0.4$ in postmenopausal women). The results were similar when we excluded two studies with breast cancer survivors from overall ($p = 0.1$) and stratified analyses ($p = 0.3$ in premenopausal women; $p = 0.4$ in postmenopausal women).

Only one randomized trial has examined the effect of an exercise intervention on breast density in postmenopausal women. In this trial, which assigned women to either an intervention arm with 1 year aerobic exercise (45 min, 5 days per week) targeting at least 150 min/week of moderate to vigorous physical activity or usual level of physical activity (control arm), found no difference in change of percent density between the arms (intervention minus control: -0.4% , $p = 0.6$) [23]. No randomized trials have been conducted in premenopausal women.

Lifetime physical activity and breast density

Only two studies examined the association of lifetime physical activity with breast density (Fig. 6; Table 2). When we combined the data (Table 3), we found no statistically significant differences in breast density at the extreme levels of lifetime physical activity either overall ($p = 1.0$) or when stratified by menopausal status ($p = 1.0$ in both pre- and postmenopausal women).

Discussion

The evidence on association of physical activity and mammographic breast density remains equivocal. We identified 20 published studies that investigated the association between physical activity and breast density. Differences in study designs, including characteristics of the study population, timing of physical activity, and breast density estimation preclude quantitative synthesis of the data via meta-analysis. Similarly, these design differences also precluded drawing conclusions as to whether design features might explain the observed differences in the results. In the following, we discuss some of those methodological issues, including physical assessment methods and associations in pre- and post-menopausal women.

Physical activity assessment

Timing, type, and dose of physical activity—The majority of the studies examined the relationship between recent physical activity and breast density. The biological relevance of physical exercise early versus later in life on breast density remains unclear. Whether physical activity could result in long-term changes in breast tissue and a subsequent reduced risk of high density later in life is unclear. Future studies would benefit from prospective

designs with data collection in adolescence and subsequent follow-up of women throughout the adulthood for their breast density assessment.

The majority of the studies assessed non-occupational physical activity only. The focus on recreational/leisure-time physical activity in most studies is unlikely to introduce substantial bias in these studies. Levels of the occupational physical activity in women are generally low and much lower than in men [24]. As a result, restricting assessment of physical activity to non-occupational is considered to cause only very little underestimation of the total activity level in women [25, 26]. Furthermore, this misclassification of overall physical activity, if any, would be non-differential in nature.

Not all of those studies that assessed the intensity of the physical activity commented if the associations for vigorous physical activity were the same as those associations for less intense activity levels. In some studies, the duration of physical activity rather than intensity was used to characterize the physical activity level [27–30]. Previous reports suggest a slightly greater reduction in breast cancer risk in women with a vigorous activity level as compared to women with moderate physical activity (18 vs. 15 %) and much greater reduction with increasing duration of exercise (30 % decrease with 6.5 h/week vs. 9 % for 2–3 h/week of activity) [17]. Similarly, two studies on physical activity and breast density observed a pattern suggestive of a dose–response relationship [27, 31].

Objective versus subjective assessment—Detailed validated questionnaires were used by most of the reviewed studies to characterize the physical activity level. These validation studies find a moderate correlation (mean 0.37, range –0.71–0.98) between self-reported and objectively measured physical activity level [32]. Thus, the potential for an exposure misclassification remains, which, depending on characteristics of the exposure and nature of the instrument, might result in either overestimation of the association or null findings. On the other hand, an objective assessment of the physical activity level, for example, with accelerometers could improve the exposure characterization, but such methods are very costly which limits their application in large epidemiologic studies.

Study populations

A vast majority of the studies on the association between physical activity and breast density had racially homogeneous populations and the majority of the studies (14 or 70 %) included predominantly white women. Thus, their findings might be limited to certain racial/ethnic subgroups. In some studies, breast density appeared to be greater in African American women as compared with white women at age 65 and younger, but did not differ by race in women older than 65 years [33]. Inclusion of sufficient number of women from racial minorities would allow to investigate the associations of physical activity and breast density by race/ethnicity.

Two studies assessed the association of physical activity with breast density in breast cancer survivors. In one of those studies, both physical activity and breast density of the contralateral breast were assessed after the breast cancer diagnosis. Even though the risk estimates were adjusted for Tamoxifen use, the time since discontinuation of Tamoxifen use was not taken into account. Whether the effect of Tamoxifen on breast density diminishes with time after cessation of Tamoxifen therapy yet needs to be determined [34–37]; some recent reports, however, suggest that the density might increase after discontinuation of Tamoxifen [37]. Thus, an adjustment for the time since Tamoxifen cessation in addition to the history of Tamoxifen use might be necessary in studies with breast cancer survivors.

All studies with significant time between the exposure and mammograms (5 years), with exception of one study [30], did not report on whether there were any women who were

premenopausal at the time of the physical activity assessment and became postmenopausal at the time of the mammogram. Breast density declines around menopause because of the breast tissue involution [2, 38] and the portion of that decline that might be attributable to the effect of physical activity is hard to measure. Among studies with a mixed population with respect to the menopausal status, only a few reported the results separately for pre- and postmenopausal women. Some studies suggest that breast density-associated breast cancer risk is different in pre- and postmenopausal women [39]. The underlying biological mechanisms by which physical activity may affect breast density could also be different in pre- and postmenopausal women owing to the differences in the breast tissue proliferation rates [40, 41] and estrogen synthesis before and after menopause [42–44]. Due to these issues, reporting the results separately for pre- and post-menopausal women becomes important.

The studies in premenopausal women did not all assess breast density in the same phase of the menstrual cycle. A few authors have reported changes in breast density during the menstrual cycle [45, 46]. Thus, an adjustment for the phase of the menstrual cycle in premenopausal women or a consistent collection of the mammogram data in one phase is preferable. Finally, some studies in postmenopausal women have not adjusted their risk estimates to the use of hormone replacement therapy, a known and strong risk factor for high breast density [9, 12, 47–59].

Other considerations

Success in revealing true associations depends on variability of the exposure and outcome in the study population. In some studies, the levels of physical activity in their study populations were very low [27, 31]. Similarly, other studies reported having a high proportion of women with low-risk density patterns [21]. The lack of variation in physical activity and in breast density in the study population could attenuate true associations.

All studies adjusted their risk estimates for BMI; some studies also performed analyses stratified by BMI and/or commented on the interaction between physical activity and BMI. In many studies, the observed associations either disappeared or became weaker after the adjustment for BMI. Modification of the association by BMI has also been suggested [60]. Previous studies consistently reported an inverse association of BMI with breast density [9, 47–49, 56–58, 61–71] and physical activity is inversely correlated with BMI (0.31 unit decrease in BMI per one-category increase in the physical activity index, 95 % CI 0.23–0.38) [72]. Because the association of BMI and breast density is well-described and because the potential pathway from physical activity to breast cancer includes changes in body fat, adjustment for BMI is essential in the studies between physical activity and breast density.

Conclusions

We found no evidence of association between physical activity and breast density across the studies included in this review, which might be explained by heterogeneity of the studies. Given the strength of the relationship between physical activity and breast cancer and the null findings of this review, it is unlikely that the effect of physical activity is mediated through an effect on breast density.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Graham Colditz is supported by American Cancer Society's Clinical Research Professorship and U54 CA155496 from the National Cancer Institute's Centers for Transdisciplinary Research on Energetics and Cancer (TREC). Dr. Kathleen Wolin is supported by grants RO1CA 148791 and U54 CA155496 from the National Cancer Institute and the Barnes Jewish Hospital Foundation. Dr. Yaghjian is supported by Barnes Jewish Hospital Foundation.

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Fig. 1.
Flow diagram of the literature search

Fig. 2.
Breast density at the lowest (*upper bar*) and highest (*lower bar*) extremes of physical activity

Does not include the study by Reeves et al. (80) which reports adjusted beta=0.06 (increase in density per each additional MET-h/wk of physical activity)

Does not include the study by Reeves et al. (80) which reports results being the same in pre-and postmenopausal women as the overall results (increase in density per each additional MET-h/wk of physical activity) as well as studies by Jeffreys (77) and Tseng (84) which do not report results by menopausal status

Fig. 3.
Results of the studies on association between adolescent physical activity and adult breast density, overall and by menopausal status

Does not include the study by Reeves et al. (80) which reports increase in density per each additional MET-h/wk of physical activity

Does not include the study by Reeves et al. (80) which reports results being the same in pre- and postmenopausal women as the overall results (increase in density per each additional MET-h/wk of physical activity) as well as a study by Marmara et al. (21) that reports nORs<0

Fig. 4. Results of the studies on association between past physical activity (5+ years before mammogram) and breast density, overall and by menopausal status

Does not include the study by Reeves et al. (80) which reports increase in density per each additional MET-h/wk of physical activity; the study by Contory et al. (30) which reports a reduced decline in percent density by per 1-unit increase in physical activity; the study by Wolin et al. (81) which reports 0.002 point decrease in density per 100 MET-min/wk increase in physical activity

Does not include the study by Reeves et al. (80) which reports results being the same in pre-and postmenopausal women as the overall results (increase in density per each additional MET-h/wk of physical activity); the study by Wolin et al. (81) and Suijkerbuijk et al. (78) which do not report the results by menopausal status; the study by Oestreicher et al. (28) (2.62 unit decrease in density in women with above median activity level vs. women with below median activity level); Woolcott et al. (23) (reports difference in exercise vs. control density change between baseline and 1 year follow up)

Fig. 5.
Results of the studies on association between recent physical activity and breast density, overall and by menopausal status

Fig. 6.
Results of the studies on association between recent physical activity and breast density, overall and by menopausal status

Table 1

Summary characteristics of the studies on association between physical activity/inactivity and mammographic breast density

Study characteristic	<i>n</i> (%)	Sample size	Total sample range size across all studies
Study population			
Breast cancer survivors	2 (10)	474–522	996
Healthy women			
Premenopausal/Perimenopausal ^a	14 (70)	68–1741	5,345
Postmenopausal	17 (80)	110–1,520	11,324
Race/ethnicity			
Predominantly White	14 (70)	320–2,720	15,262
Hispanic only	2 (10)	95–294	389
Asian only	1 (5)	201	201
Mixed	3 (15)	375–772	1,869
Study design			
Randomized controlled trial	1 (5)	320	320
Prospective	3 (15)	722–1,666	3,160
Case-control	1 (5)	400	400
Cross-sectional	15 (75)	95–2,720	13,860
Physical activity/inactivity recalled from ^b			
Current or within previous 5 years ^c	14 (70)	95–2,720	11,052
Past (5+ years before the mammogram)	4 (20)	375–1,666	3,493
Between age 7 and 20 (adolescent)	5 (25)	375–1,893	3,825
Lifetime history	2 (10)	375–1,900	2,275
Breast density assessment approach			
Percent breast density (continuous)	13 (65)	95–1,900	10,109
Categorical breast density	7 (35)	201–2,720	7,631

^aThree studies did not report the number of pre- and postmenopausal women in the study population

^bOne study did not specify the timing of physical activity assessment; some studies are included in more than one category

^cIncludes a randomized controlled trial with duration of 1 year

Table 2
Summary description of the studies on association between physical activity/inactivity and mammographic breast density

References	Country	Sample size	N pre-or peri/post-	Physical activity/inactivity assessment method	Timing of physical activity	Breast density assessment
Woolcott et al. [23]	Canada	320	0/320	Intervention: 45 min, 5/week; control: usual lifestyle	Current/recent (intervention > 1 year)	Percent breast density, total dense area, and total non-dense area
Oestreicher et al. [28]	USA	772	772/0	Self-reported physical activity instrument (Kaiser Physical Activity Survey)	Current/recent	Percent breast density and total dense area
Masala et al. [73]	Italy	1,666	610/1,056	Self-administered questionnaire	Past	Wolfe's classification
Controy et al. [30]	USA	722	300/422 ^a	Self-administered questionnaire	Current/recent	Percent breast density, total dense area, and total non-dense area
Sala et al. [20]	UK	400	68/313 ^b	Self-administered questionnaire	Not specified	Wolfe's classification
Gram et al. [31]	Norway	2,720	1741/979 ^c	Self-administered questionnaire	Current/recent and past	Tabar's classification
Vachon et al. [62]	USA	1,900	380/1,520 ^c	Interviewer-administered phone interview	Lifetime	Percent breast density
Lopez et al. [19]	USA	294	105/189	Interviewer-administered questionnaire	Current/recent	Percent breast density
Jeffreys et al. [74]	UK	628	NR	Self-administered questionnaire	Adolescent	Six-category (Boyd) classification
Suikerbuijk et al. [75]	The Netherlands	616	130/429 ^b	Self-administered questionnaire	Current/recent	Percent breast density and total dense area
Irwin et al. [60]	USA	474	151/323	29-item, Interviewer- administered questionnaire	Current/recent	Percent breast density, total dense area, and total non-dense area
Siozon et al. [76]	USA	375	148/227	Interviewer-administered questionnaire	Lifetime, adolescent current/recent, past	Percent breast density and total dense area
Reeves et al. [77]	USA	728	180/548	Self-administered questionnaire	Adolescent, current/recent and past	Percent breast density, total dense area, and total non-dense area
Sellers et al. [29]	USA	1,893	451/1,442	Self- administered questionnaire	Adolescent	Percent breast density
Wolin et al. [78]	USA	95	NR	27-item, self-administered physical activity instrument	Current/recent	Percent breast density
Irwin et al. [79]	USA	522	0/522	29-item, Interviewer- administered questionnaire	Current/recent	Percent breast density, total dense area, and total non-dense area
Samimi et al. [80]	USA	1,398	369/1,029	Self-administered questionnaire	Current/recent	Percent breast density
Peters et al. [27]	UK	1,292	0/1,292	Self-administered questionnaire	Current/recent	Six-category (Boyd) classification
Marmara et al. [21]	Greece	724	0/724	29-item, Interviewer- administered questionnaire	Current/recent	BI-RADS
Tseng et al. [81]	USA	201	91/110	Self- administered questionnaire	Adolescent	BI-RADS categories

NR Not reported

^aBased on the data from the visit closest to the index mammogram

^bExcludes women with missing data
^cEstimated from reported percents

Table 3

Results of Mann–Whitney tests for combined results across the studies

Timing of physical activity	All women	Premenopausal women	Postmenopausal women
Adolescent			
Included studies	Reeves, Jeffreys, Sellers, Tseng, Siozon ^a	Reeves, ^b Siozon, Sellers	Reeves, ^b Siozon, Sellers
<i>p</i> value	0.6	1.0	0.6
Early life (5 + years before mammogram)			
Included studies	Reeves, ^b Masala, Gram, Siozon ^a	Reeves, ^b Masala, Gram, Siozon	Reeves, ^b Masala, Gram, Siozon
<i>p</i> value	1.0	1.0	0.2
Recent			
Included studies	Reeves, ^b Conroy, Gram, Suijkerbuijk, Irwin, 2006 Wolin, Samimi, ^a Siozon ^a	Reeves, ^b Oestreich, Conroy, ^b Gram, Irwin, 2006, Siozon, Samimi	Reeves, ^b Woolcott, Conroy, ^b Gram, Suijkerbuijk, Irwin, 2006, Siozon, Irwin, 2007, ^a Samimi, Peters
<i>p</i> value	0.6 (0.1 ^c)	0.1 (0.3 ^c)	0.4 (0.4 ^c)
Life long			
Included studies	Vachon, ^d Siozon ^a	Vachon, Siozon	Vachon, Siozon
<i>p</i> value	1.0	1.0	1.0

Note. Does not include studies by Sala et al. [20] (did not report the timing of physical activity), Lopez et al. [19] (investigation of association between inactivity and breast density) and Marmara et al. [21] (reported ORs values < 0 and 95 % CIs sometimes not centered around the point estimate)

^aWeighted averages of adjusted mean densities calculated from estimates reported by menopausal status (Siozon and Samimi) or BMI categories (Irwin et al. [79])

^bResults were either reported or stated to be similar by the timing of physical activity and/or menopausal status without showing the data

^c*p* value for the test excluding studies with breast cancer patients

^dEven though the overall results cannot be extrapolated, the direction of association is the same in both pre- and postmenopausal women and the overall results are treated as being also in the same direction