Recreational Physical Activity and Mammographic Breast Density Characteristics

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Abstract

Increased mammographic breast density is considered an intermediate marker of breast cancer risk. Physical activity is believed to reduce breast cancer risk; however, its effect on breast density is not well understood. We studied the association between recreational physical activity and mammographic characteristics of the breast among a population of premenopausal and postmenopausal women enrolled as controls (n = 728) in a case-control study of mammographic breast density and breast cancer. Women were enrolled shortly after obtaining their regular screening mammograms, and participants reported their current and lifetime recreational physical activity history using a self-administered, reliable questionnaire at study enrollment. Linear regression was used to determine associations between physical activity variables and the dense breast area, non-dense area, total breast area, and percent density. Age-adjusted analyses revealed significant inverse associations between physical activity variables and the non-dense area and total area and positive associations with percent breast density. These associations were attenuated and nonsignificant after adjustment for body mass index (BMI). Adjustment for additional factors did not substantially change the results. Physical activity was not associated with the dense breast area before or after adjustment for BMI. Self-reported recreational physical activity was not significantly associated with the mammographic characteristics of the breast after adjustment for BMI in this population. These results suggest that the mechanism by which physical activity reduces breast cancer risk may not involve breast density. (Cancer Epidemiol Biomarkers Prev 2007;16(5):934–42)

Introduction

Breast cancer accounts for nearly one third of all cancers diagnosed among women in the United States and is the second leading cause of cancer mortality in this population (1). Although mortality from breast cancer decreased ~2.3% each year in recent years, the incidence of breast cancer increased ~0.3% each year during the same time period, likely due to broader use of mammography and detection of cancers that would not be found otherwise (2). To reduce the incidence of breast cancer, an improved understanding of its causal factors and the ability to intervene on such factors to prevent disease are needed.

The composition of the breast varies by individual. Fat tissue is radiolucent and appears dark on a mammogram, whereas epithelial and connective tissues are radiodense and appear bright. Breast density is determined by how much epithelial and connective tissue are present relative to fat (3-6). The density of the breast is qualitatively categorized into parenchymal patterns as described by Wolfe (7) or quantitatively reported as the percentage of the breast occupied by dense tissue. Mammographic breast density is positively associated with breast cancer risk using both qualitative (7-14) and quantitative (9, 14, 15) measurements. Mammographic breast density changes in response to factors such as age (16, 17) and use (18, 19) or cessation (20) of hormone therapy. Because of its strong association with breast cancer risk and its ability to be modified, much attention has focused on mammographic breast density as an intermediate marker for breast cancer.

Few studies have investigated the relationship between physical activity and mammographic breast density; yet, physical activity is believed to be an important and modifiable risk factor for breast cancer. The IARC determined that ~10% of all breast cancers are related to lack of adequate physical activity (21). The Women's Health Initiative (WHI) Observational Study also reported that increased levels of recreational physical activity were related to decreased risk of breast cancer, with an 18% reduction in breast cancer risk from brisk walking for 1.25 to 2.5 h/wk (22). Eight reports to date have described the relationship between physical activity and mammographic breast density: one prospective (19) and four cross-sectional studies (23-26) reported no statistically significant association; one cross-sectional study of Hispanic women found a positive association with physical *inactivity* (27); and cross-sectional analyses conducted in a study of breast cancer survivors reported an inverse association between pre-diagnosis breast density and physical activity among obese postmenopausal women only (28), with a similar association observed 2 to 3 years after diagnosis (29). The methods of physical activity assessment as well as the characteristics of the study populations have varied widely among these studies, however.

Further research is necessary to elucidate the effect of physical activity on breast density and to determine if this relationship varies by breast cancer risk, body mass index (BMI), and/or other personal characteristics. Using the physical activity measure employed by the WHI (22), we evaluated associations between recreational physical activity and mammographic breast density among a group of premenopausal and postmenopausal women receiving screening or diagnostic mammograms.

Materials and Methods

Study Population. This study is a cross-sectional analysis of participants included as control women from a case-control

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Table 1. Descriptive characteristics of MAMS control study population, Pittsburgh, PA 2001-2005 (n = 728)

Characteristic	Benign (n = 224), n (%)	Well (n = 504), n (%)	P
Age, y*	54.2 (9.1)	58.7 (9.9)	<0.0001
Age, y			
<50	78 (34.8)	88 (17.5)	<0.0001
50-59	77 (34.4)	201 (39.9)	
60-69	57 (25.5)	136 (27.0)	
≥70	12 (5.4)	79 (15.7)	
BMI, kg/m^2*	27.7 (6.3)	28.8 (7.1)	0.04
BMI, kg/m^2			
Normal, <25	83 (37.1)	168 (33.3)	0.19
Overweight, 25 to <30	76 (33.9)	162 (32.1)	
Obese, ≥30	64 (28.6)	174 (34.5)	
Race/ethnicity			
White	211 (94.2)	474 (94.1)	0.94
Other	13 (5.8)	30 (6.0)	
Education			
≤High school	60 (26.8)	111 (22.0)	0.16
Post-secondary education	164 (73.2)	393 (78.0)	
Smoking status			
Never	125 (55.8)	302 (59.9)	0.002
Former	66 (29.5)	169 (33.5)	
Current	33 (14.7)	33 (6.6)	
Alcohol intake in year before enrollment			
No regular consumption	161 (71.9)	364 (72.2)	0.05
<12 g/d	30 (13.4)	84 (16.7)	
≥12 g/d	21 (9.4)	47 (9.0)	
Current alcohol drinker			
No	161 (71.9)	364 (72.2)	0.05
Yes	52 (23.2)	131 (26.0)	
Hormone therapy use status			
Never	98 (43.8)	238 (47.2)	<0.0001
Former	50 (22.3)	207 (41.1)	
Current	76 (33.9)	59 (11.7)	
Age at menarche, y			
<12	44 (19.6)	98 (19.4)	0.01
12	52 (23.2)	156 (31.0)	
13	91 (40.6)	142 (28.2)	
≥14	37 (16.5)	107 (21.2)	
Menopausal status			
Premenopausal	76 (33.9)	104 (20.6)	0.0001
Postmenopausal	148 (66.1)	400 (79.4)	
Age at menopause, y			
Premenopausal	76 (33.9)	104 (20.6)	0.0001
<40	13 (5.8)	24 (4.8)	
40-44	21 (9.4)	50 (9.9)	
45-49	51 (22.8)	94 (18.7)	
50-54	51 (22.8)	201 (39.9)	
≥55	7 (3.13)	23 (4.6)	
No. live births			
None	43 (19.2)	104 (20.6)	0.61
1	26 (11.6)	64 (12.7)	
2	79 (35.3)	161 (31.9)	
3	50 (22.3)	99 (19.6)	
≥4	26 (11.6)	76 (15.1)	
Age at first pregnancy lasting over 6 mo			
No live births/pregnancy lasted <6 mo	43 (19.2)	105 (20.8)	0.49
<20	24 (10.7)	42 (8.3)	
20-24	70 (31.3)	151 (30.0)	
25-29	59 (26.3)	117 (23.2)	
≥30	27 (12.1)	86 (17.1)	
History of breast-feeding			
Not applicable	43 (19.2)	105 (20.8)	0.47
No	82 (36.6)	178 (35.3)	
Yes	98 (43.8)	221 (43.9)	
First-degree relative with breast cancer			
No	181 (80.8)	423 (83.9)	0.25
Yes	43 (19.2)	78 (15.5)	
Ever had previous breast biopsy			
No	140 (62.5)	440 (87.3)	<0.0001
Yes	83 (37.1)	64 (12.7)	
No. previous breast biopsies			
None	141 (63.0)	440 (87.3)	<0.0001
1	53 (23.7)	45 (8.9)	
≥2	28 (12.5)	18 (3.6)	

NOTE: Percentages may not sum to 100% due to rounding or missing data.
*Reported as mean (SD).

Table 2. Summary of self-reported recreational physical activity in the MAMS control study population

Categorical variables	Benign (n = 224), n (%)	Well (n = 504), n (%)	P
History of mild exercise*			
Age 18	128 (60.7)	300 (60.6)	0.99
Age 35	141 (66.5)	319 (63.7)	0.47
Age 50 †	64 (47.4)	236 (57.0)	0.05
History of moderate exercise*			
Age 18	124 (57.9)	280 (56.2)	0.67
Age 35	135 (62.8)	293 (58.5)	0.28
Age 50 †	51 (37.0)	216 (52.2)	0.002
History of strenuous exercise*			
Age 18	88 (40.6)	223 (44.7)	0.30
Age 35	96 (44.0)	242 (48.2)	0.30
Age 50 †	29 (20.3)	133 (32.0)	0.008
Cumulative exercise, MET-h/wk			
No activity	36 (16.1)	55 (10.9)	0.10
≤5	56 (25.0)	111 (22.0)	
5.1-10	32 (14.3)	76 (15.1)	
10.1-20	54 (24.1)	112 (22.2)	
20.1-40	35 (15.6)	112 (22.2)	
≥40	11 (4.9)	38 (7.5)	
Mild exercise, h/wk			
No activity	92 (41.1)	204 (40.5)	0.52
<1	48 (21.4)	124 (24.6)	
1.1-2	40 (17.9)	83 (16.5)	
2.1-4	36 (16.1)	65 (12.9)	
≥4	8 (3.6)	28 (5.6)	
Moderate or strenuous activity, h/wk			
No activity	120 (53.6)	218 (43.3)	0.03
<1	40 (17.9)	81 (16.1)	
1.1-2	26 (11.6)	85 (16.9)	
2.1-4	28 (12.5)	77 (15.3)	
≥4	10 (4.5)	43 (8.5)	
Calculated variables	**Mean (SD)**	**Mean (SD)**	**P**
Mild exercise, MET-h/wk	3.2 (4.4)	3.3 (4.8)	0.79
Moderate exercise, MET-h/wk	2.2 (4.2)	3.1 (4.9)	0.02
Strenuous exercise, MET-h/wk	3.1 (7.7)	4.4 (8.8)	0.06
Walking, MET-h/wk	4.5 (6.6)	4.9 (6.3)	0.41
Cumulative exercise, MET-h/wk	13.0 (15.5)	15.7 (16.7)	0.04

*Missing values were excluded for the statistical calculations for history of exercise at ages 18, 35, and 50.
†Includes only the 146 benign and 416 well women who were ≥50 y old.

study of hormonal determinants of mammographic breast density, the Mammograms and Masses Study (MAMS). Recruitment for MAMS took place from 2001 to 2005. Women were eligible for MAMS if they were age ≥18 and either (*a*) were receiving a breast biopsy or an initial surgical consultation after a diagnosis of breast cancer at Magee-Womens Hospital, Pittsburgh, PA or (*b*) were receiving a routine screening mammogram at a Magee-Womens Hospital mammography screening clinic throughout the greater Pittsburgh region. Women were excluded from MAMS if they met one or more of the following exclusion criteria: (*a*) reported a prior history of cancer other than nonmelanoma skin cancer, (*b*) drank more than 5 alcoholic beverages per day, or (*c*) weighed either <110 or >300 lbs.

Women recruited from the biopsy clinic who were determined to have a benign breast lesion were eligible as ''benign'' controls. Of the 856 women approached at the time of biopsy, 573 (67%) enrolled in the study and 313 (55%) of the enrolled women were counted as ''benign'' controls. A second control group (''well'' controls) was selected from women receiving routine screening mammograms. Well controls were recruited through presentations given by research staff in the mammogram clinic waiting room or by flyers describing MAMS included with the mammogram reports sent to women with a negative mammogram. Of 100 women approached through the in-clinic presentations, 85 (85%) were enrolled in the study as ''well'' controls. A total of 21,606 flyers were sent, and 1,025 responses were received (5%). Of the respondents, 857 (84%) were eligible, and 471 (55%) enrolled in the study as ''well'' controls. This study was approved by the Institutional Review Board at the University of Pittsburgh. All participants provided written informed consent. The final study population consisted of 1,133 women, including 264 cases, 313 benign controls, and 556 well controls.

Table 3. Summary of mammographic breast density characteristics in the MAMS control study population, age adjusted

Variable	Benign (n = 224), age-adjusted mean (SE)	Well (n = 504), age-adjusted mean (SE)	P
Interval between mammogram and questionnaire, d*	47.0 (4.6)	38.7 (3.0)	0.13
Dense area of breast, cm^2	50.0 (1.9)	42.7 (1.3)	0.002
Non-dense area of breast, cm^2	103.4 (5.0)	112.8 (3.3)	0.12
Total area of breast, cm^2	153.4 (5.1)	155.5 (3.4)	0.73
% Breast density	37.0 (1.3)	32.4 (0.9)	0.004

*Mean reported is for the absolute value of the interval.

Table 4. Bivariate associations between recreational physical activity variables and breast density variables, benign controls (n = 224)

Recreational physical activity variable	Dense area		Non-dense area		Total breast area		% Density	
	Mean (SD)	P	Mean (SD)	P	Mean (SD)	P	Mean (SD)	P
Cumulative exercise, MET-h/wk								
No activity	54.3 (33.4)	0.97	134.8 (81.0)	0.02	189.1 (86.2)	0.007	31.8 (17.4)	0.44
≤5	51.4 (34.4)		100.1 (74.7)		151.5 (77.6)		39.1 (21.0)	
5.1-10	51.4 (25.3)		99.5 (76.2)		150.9 (80.4)		39.3 (18.8)	
10.1-20	49.0 (28.8)		85.1 (51.5)		134.1 (50.1)		39.2 (20.4)	
20.1-40	50.1 (27.2)		95.1 (69.8)		145.3 (74.2)		39.9 (20.7)	
≥40	46.8 (25.5)		67.2 (34.7)		114.0 (34.6)		42.5 (17.8)	
Mild exercise, h/wk								
No activity	54.1 (33.2)	0.39	114.2 (75.3)	0.04	168.3 (80.1)	0.02	35.3 (19.1)	0.07
<1	52.4 (31.2)		79.8 (61.9)		132.2 (59.8)		44.7 (21.9)	
1.1-2	47.1 (26.5)		104.4 (69.1)		151.5 (72.9)		36.3 (19.7)	
2.1-4	47.9 (24.9)		89.4 (55.9)		137.3 (61.7)		37.8 (16.9)	
≥4	36.0 (13.8)		72.5 (94.2)		108.5 (84.4)		45.6 (21.1)	
Moderate or strenuous exercise, h/wk								
No activity	49.5 (30.6)	0.70	108.0 (74.0)	0.15	157.5 (75.0)	0.18	36.1 (20.0)	0.37
<1	57.2 (32.7)		97.2 (77.1)		154.4 (88.8)		41.1 (16.8)	
1.1-2	50.0 (27.7)		73.2 (46.9)		123.2 (43.9)		43.5 (22.0)	
2.1-4	49.6 (27.0)		100.4 (66.5)		150.0 (71.0)		37.9 (21.0)	
≥4	48.0 (26.8)		74.3 (36.3)		122.4 (38.4)		40.4 (18.8)	

NOTE: P from ANOVA.

Only women who were enrolled as controls (either benign or well) were eligible for inclusion in the present analyses. We further excluded 114 women without mammogram data (66 benign and 48 well) and 27 women without physical activity data (23 benign and 4 well). Thus, 728 women were included in these analyses (224 benign and 504 well). Women who were excluded from the analysis were of similar age, ethnicity, and BMI as those included.

Data Collection. At enrollment, participants completed a self-administered questionnaire that collected extensive data including demographic factors and medical, medication, menstrual, hormone therapy use, reproductive, oral contraceptive use, family cancer, weight, recreational physical activity, smoking, and alcohol use histories. Height and weight were measured by a study nurse using a stadiometer and a standard balance beam scale while participants were wearing light clothing and no shoes. Height and weight were used to calculate BMI (weight in kilograms divided by height in meters squared). Age at menopause was calculated according to methods outlined by the WHI (30).

Recreational Physical Activity Assessment. Participants were asked about their usual levels of recreational physical activity (henceforth referred to as ''physical activity'') at the time of questionnaire completion and at specific previous ages using the physical activity measure employed and tested in the WHI (22, 31). Women were first asked about the frequency, intensity, and duration of walking outside the home. The frequency categories for walking were rarely or never, one to three times each month, two to three times each week, four to six times each week, and seven times or more each week. Women were also asked to indicate the speed at which they normally walked: casual strolling or walking (<2 miles/h), average or normal (2-3 miles/h), fairly fast (3-4 miles/h), or very fast (>4 miles/h). Participants were then asked about the frequency and duration of exercise other than walking: mild (e.g., slow dancing or bowling), moderate (e.g., biking outdoors or easy swimming), or strenuous (e.g., aerobics or jogging). Frequency categories for mild, moderate, and strenuous exercise were none, 1 day/wk, 2 days/wk, 3 days/wk, 4 days/wk, and ≥5 days/wk. Duration categories for both walking and the three levels of exercise were <20 min, 20 to 39 min, 40 to 59 min, and ≥1 h. Finally, participants reported if they usually did mild, moderate, or strenuous exercise at least thrice a week at ages 18, 35, and 50.

Hours exercised per week and metabolic equivalent (MET) hours per week were calculated following the algorithms used in the WHI (22). Midpoint values were calculated for each category of frequency and duration, and these values were multiplied to calculate hours exercised per week. MET values were assigned to each level of activity: mild exercise, 3 MET; moderate exercise, 4 MET; and strenuous exercise, 7 MET. Average or normal speed walking was assigned a value of 3 MET; fast walking was assigned a value of 4 MET; and very fast walking was assigned a value of 4.5 MET. These MET values were multiplied by the values of hours exercised per week for each type of activity to determine MET-h/wk. A cumulative measure of current physical activity was calculated by summing the values for MET-h/wk over all four levels of physical activity (walking, mild, moderate, and strenuous exercise).

Mammographic Density Measurement. Copies of original screening mammograms were obtained with the permission of the participants and sent to Martine Salane, an expert reader (32-34), to determine mammographic density. Dense breast area was measured by outlining areas of mammographic density on the craniocaudal view, excluding biopsy scars, Cooper's ligaments, and breast masses. Total breast area and outlined dense regions were computed using a compensating polar planimeter (LASICO). Percentage of breast density was calculated by dividing the area of the outlined dense region by the total area of the breast. A subjective measure of film quality was also reported. To determine reproducibility of the readings, a random sample of 28 mammograms was reevaluated at a later time (8 from the lowest tertile of percent breast density and 10 each from the remaining two tertiles of percent breast density). The intraclass correlation coefficient for intra-observer agreement was ρ = 0.86 for the continuous measurement of dense area, ρ = 0.99 for total area, and ρ = 0.89 for percent breast density. Our intraclass correlation coefficient for percent density is consistent with Salane's reproducibility in the Breast Cancer Detection Demonstration Project (intraclass correlation coefficient ρ = 0.915 for 193 sets of films; ref. 34).

Statistical Analysis. Comparisons between benign and well controls were done using two-sample t tests for continuous measures and the χ^2 test for discrete measures. The cumulative MET values were analyzed as continuous variables, and other categorical physical activity variables were grouped for analysis as in the WHI (22). Mild, moderate, and strenuous

activities at ages 18, 35, and 50 were captured as yes/no variables. ANOVA was used to compare the mean dense area, non-dense area, total area, and percent breast density across the levels of the physical activity variables. For the ANOVA analyses only, the continuous MET values were categorized as in the WHI: no activity, <5, 5.1 to 10, 10.1 to 20, 20.1 to 40, and ≥40 MET-h/wk (22).

Separate multivariable linear regressions were done using dense area, non-dense area, total breast area, and percent breast density as dependent variables and the physical activity variables as the independent variable of interest. Regressions included only one physical activity variable at a time. The following variables were evaluated for inclusion as potential confounders in each regression as prior studies have shown associations with breast density and/or breast cancer: age (continuous), BMI (<25, 25 to <30, ≥30 kg/m^2), race (White, other), smoking status (never, former, current), alcohol intake in year before enrollment (no regular consumption, <12 g/d, ≥12 g/d), current alcohol drinker (no, yes), hormone therapy status (never, former, current), age at menarche (<12, 12, 13, ≥14), menopausal status (premenopausal, postmenopausal), age at menopause (premenopausal, <40, 40-44, 45-49, 50-54, ≥55), number of live births (none, 1, 2, 3, ≥4), age at first pregnancy lasting more than 6 months (no live births/never pregnant, <20, 20-24, 25-29, ≥30), history of breast-feeding (not applicable/no, yes), family history of breast cancer (no, yes), previous breast biopsy (no, yes), number of previous breast biopsies (none, 1, ≥2), quality of the mammographic film (excellent, good, fair, poor), and interval between questionnaire date and mammogram date (continuous). Categorizations of the previous variables were based on common cut points (e.g., BMI) or from the original response categories with collapsing of categories to prevent small cell counts (e.g., age at menarche). These covariates were first evaluated for inclusion in the models using stepwise backward regression with multiple partial F tests; variables significant at the 0.10 level were included in the final adjusted model. All analyses were stratified by control type. The physical activity variables were added to the model after the significant confounders had been identified. Dummy variables were created for categorical variables as appropriate. Mammographic density measures and MET-h/wk were normally distributed, and analyses were conducted with these variables in the natural scale. All tests done were two sided, with $P \leq 0.05$ considered statistically significant. All analyses were done using SAS version 9.1.

Results

Table 1 describes the demographic and breast cancer risk factor characteristics of the study population. Most participants in this analysis were well controls (69.2%), and benign and well controls differed significantly on most demographic characteristics. The average age varied by control type, with benign controls having a mean age of 54.2 (SD, 9.1; range, 40-84) and well controls having a mean age of 58.7 (SD, 9.9; range, 36-85; $P < 0.0001$). The vast majority (99.6%) of participants was age 40 or older and thus in the age group for which annual mammograms are recommended. Three well controls were below the typical screening age: two were age 39 and one was age 36 at the time of enrollment. Benign controls were more likely to be current smokers (14.7% versus 6.6%, $P = 0.002$) and current users of hormone therapy (33.9% versus 11.7%, $P < 0.0001$). Menopausal status also varied by control type, with 33.9% of benign controls and 20.6% of well controls being premenopausal ($P = 0.0001$). The vast majority (94%) of the study population was White, and this did not differ by control type.

The reported current and past levels of recreational physical activity are displayed in Table 2. History of exercise did not vary by control type, except for history of mild, moderate, or strenuous exercise at age 50. Benign controls were less likely to report engaging in physical activity at this age (this comparison included only women who were age 50 or older at the time of the survey). The reported cumulative MET hours of exercise per week was an average of 13.0 (SD, 15.5; range, 0.0-110.8) among benign controls and 15.7 (SD, 16.7; range, 0.0-110.3) for well controls ($P = 0.04$). Approximately 16% of benign controls and 11% of well controls reported engaging in no exercise, and about 20% of benign controls and 30% of well controls reported >20 cumulative MET-h/wk. The distributions of current exercise in the population were somewhat positively skewed, with 30.8% of benign controls and 38.3% of well controls having greater than the overall mean MET-h/wk of walking (4.76; SD, 6.40) and only 18.3% of benign controls

Table 5. Bivariate associations between recreational physical activity variables and breast density variables, well controls (n = 504)

Recreational physical activity variable	Dense area		Non-dense area		Total breast area		% Density	
	Mean (SD)	P	Mean (SD)	P	Mean (SD)	P	Mean (SD)	P
Cumulative exercise, MET-h/wk								
No activity	45.0 (28.6)	0.06	143.1 (77.2)	<0.0001	188.1 (73.2)	<0.0001	26.5 (17.1)	<0.0001
≤5	41.4 (27.3)		129.6 (84.6)		171.0 (82.7)		29.5 (19.3)	
5.1-10	41.7 (34.8)		113.0 (71.4)		154.7 (73.8)		30.6 (23.1)	
10.1-20	37.3 (23.7)		124.0 (80.4)		161.3 (78.9)		28.2 (18.4)	
20.1-40	48.4 (26.4)		85.3 (57.9)		133.7 (61.4)		40.2 (20.0)	
≥40	39.3 (20.4)		90.3 (66.6)		129.6 (72.4)		34.0 (17.0)	
Mild exercise, h/wk								
No activity	39.8 (27.5)	0.26	125.1 (80.5)	0.02	164.8 (79.0)	0.04	28.8 (19.4)	0.08
<1	43.6 (30.4)		117.0 (83.6)		160.5 (85.0)		33.2 (21.7)	
1.1-2	45.8 (26.7)		100.0 (55.9)		145.8 (58.8)		33.6 (17.6)	
2.1-4	40.7 (23.7)		93.9 (59.9)		134.6 (57.2)		34.2 (20.3)	
≥4	49.0 (21.5)		117.7 (88.7)		166.7 (89.1)		36.1 (20.6)	
Moderate or strenuous exercise, h/wk								
No activity	43.3 (30.9)	0.57	124.0 (78.7)	0.01	167.2 (77.2)	0.009	30.0 (19.9)	0.21
<1	39.6 (24.4)		118.4 (79.9)		158.0 (78.0)		31.0 (21.3)	
1.1-2	39.5 (22.8)		107.2 (72.9)		146.8 (75.4)		32.2 (20.5)	
2.1-4	45.5 (27.8)		109.9 (78.4)		155.3 (76.1)		34.2 (20.2)	
≥4	42.8 (21.3)		81.7 (49.6)		124.5 (58.9)		36.9 (15.5)	

NOTE: P from ANOVA.

Table 6. Multivariable associations between recreational physical activity variables and breast density variables, benign controls (n = 224)

Recreational physical activity variable	Adjusted for age		Adjusted for age and BMI		Fully adjusted model*	
	β	P	β	P	β	P
Dense area						
Cumulative exercise, MET-h/wk	−0.12	0.38	−0.099	0.45	−0.097	0.45
Mild exercise, h/wk	−2.23	0.10	−2.20	0.11	−1.37	0.31
Moderate or strenuous exercise, h/wk	−0.81	0.48	−0.67	0.56	−0.60	0.59
Non-dense area						
Cumulative exercise, MET-h/wk	−0.68	0.02	−0.20	0.39	−0.18	0.44
Mild exercise, h/wk	−4.68	0.14	−2.40	0.32	−2.78	0.25
Moderate or strenuous exercise, h/wk	−3.12	0.24	1.12	0.58	0.93	0.64
Total breast area						
Cumulative exercise, MET-h/wk	−0.80	0.01	−0.30	0.23	−0.21	0.40
Mild exercise, h/wk	−6.92	0.04	−4.60	0.08	−4.40	0.08
Moderate or strenuous exercise, h/wk	−3.93	0.15	0.45	0.84	0.74	0.73
% Density						
Cumulative exercise, MET-h/wk	0.076	0.37	−0.017	0.82	−0.022	0.77
Mild exercise, h/wk	0.61	0.49	0.12	0.88	0.31	0.69
Moderate or strenuous exercise, h/wk	0.039	0.96	−0.81	0.22	−0.89	0.16

NOTE: Estimated coefficients are for a 1-unit increase in the continuous recreational physical activity variable (MET-h/wk). P from t test of coefficients.
*Variables and n included in fully adjusted model differed for each density outcome. Dense area: age, BMI, hormone therapy use, age at menarche, age at menopause, history of breast-feeding, number of breast biopsies, interval between mammogram and questionnaire (n = 215). Non-dense area: age, BMI, number of breast biopsies, quality of film (n = 222). Total breast area: age, BMI, history of breast-feeding, quality of film (n = 223). % Density: age, BMI, HT use, age at menopause, number of breast biopsies (n = 217).

and 26.8% of well controls having greater than the overall mean MET-h/wk of strenuous exercise (3.99; SD, 8.49; data not shown).

On average, a woman's mammogram was taken within 47 and 39 days of questionnaire completion for benign and well controls, respectively (Table 3). The age-adjusted average percent breast density in the population was 37.0% (SE, 1.3%) for benign controls and 32.4% (SE, 0.9%) for well controls (P = 0.004). Overall, very few of the films were considered to be of poor quality (8.2%), and the quality of films did not vary by control type.

For both benign and well controls, age-adjusted associations between current physical activity and breast density characteristics were apparent for the non-dense area, total breast area, and percent density but were generally not significant for the outcome of dense area (Tables 4 and 5). Selected results of the linear regressions are displayed in Tables 6 and 7. Similar results were observed among benign and well controls. Although a modest positive association was found between hours per week of mild exercise and dense area among well controls (P = 0.04), no significant associations were observed between cumulative MET hours of exercise per week or hours of moderate and strenuous activity per week and the dense breast area in models adjusted for age only, age and BMI, or in the fully adjusted models. Similarly, no associations were observed between the other physical activity variables investigated and the size of the dense breast area (data not shown). In both benign and well controls, significant inverse associations were observed between many current and lifetime physical activity variables and the non-dense area and total breast area and positive associations with percent density, but only when adjusted for age. These associations were all attenuated after further adjustment for BMI. Overall, additional adjustment for other covariates did not substantially change the results. However, a statistically significant association was observed between hours of mild activity per week and percent density among well controls, with a 1.33 unit increase in percent density for each additional hour of mild exercise (P = 0.005). In general, similar results were observed for physical activity at ages 18, 35, and 50 and for MET hours of mild, moderate, strenuous, and walking exercise (data not shown).

Similar results were obtained when restricting analyses to women whose mammogram was taken within 6 months of their questionnaire date (97.3% of the study population) and when stratifying by menopausal status (data not shown).

Discussion

Although measures of current and past recreational physical activity were significantly associated with non-dense breast area, total breast area, and percent breast density in age-adjusted analyses, adjustment for BMI attenuated these results. Significant positive associations between hours of mild exercise per week and both dense area and percent density were observed among well controls in multivariable models; however, given the number of statistical comparisons, lack of other significant associations, and the inconsistency of this finding with all prior studies of physical activity and mammographic density (19, 23-29), these findings are likely due to chance. Physical activity was not significantly associated with dense breast area before or after adjustment for BMI.

Overall, the present findings are consistent with those of previous studies of recreational physical activity and breast density, most of which have reported no statistically significant association (19, 23-26). Also similar to our findings, Siozon et al. showed that associations between physical activity and breast density were no longer significant after adjusting for BMI (26). Conversely, two studies conducted in distinct populations have reported results consistent with an inverse association between physical activity and breast density (27-29). In a multi-ethnic study of 474 U.S. women, Irwin et al. reported that higher levels of sports/recreational physical activity were associated with lower dense breast area and percent density among obese postmenopausal women [mean (SD) MET-h/wk = 7.8 (12.6)] yet were associated with an increase in percent density among nonobese premenopausal women [mean (SD) MET-h/wk = 19.4 (21.8); ref. 28]. Although activity levels in these two subgroups are similar to the mean MET-h/wk observed in the comparable subgroups of women in MAMS, we did not observe significant associations with dense breast area or percent density when stratifying analyses by menopausal status. The Irwin et al. results may not be generalizable to cancer-free women, however, as the participants were

women currently diagnosed with breast cancer, recalling their physical activity in the year before diagnosis, and the prediagnostic mammograms included in the study may have contained subclinical disease. Lastly, among 294 Hispanic women in Chicago, Lopez et al. observed higher percent breast density for women reporting at least 3.5 h/d of physical inactivity, defined as the average number of hours per day spent watching television, reading, knitting, or using a computer (27). These results may not be generalizable to non-Hispanic women; Mexican-American women report more physical inactivity than non-Hispanic Whites (35). However, we are unable to compare these results with those of the present study as we did not obtain a measure of physical *inactivity*.

Apart from lack of a true association between physical activity and mammographic density, an alternative explanation for the null findings is that physical activity may actually reduce absolute breast density, but studies thus far have been unable to detect such an association (28). Overall, levels of physical activity are fairly low in many populations. In our study, 13% of the total population of women reported no current physical activity, and only 24% reported a level of weekly strenuous activity that was greater than the mean. Similarly, of the non-cases in the WHI Observational Study, 13% reported no current physical activity, and 35% reported no current moderate or strenuous physical activity (22). National data show that 39.5% of adult women report no leisure-time physical activity, and only 30.6% report regular leisure-time activity (36). Indeed, the levels of physical activity needed to observe a significant change in breast density may be higher than are typical of most U.S. women.

The observed lack of an association between physical activity and breast density is surprising in light of the convincing evidence for a decreased risk of breast cancer with increasing levels of physical activity (21). Indeed, a previous analysis of data from the WHI, which employed the same questions and algorithms for assessing recreational physical activity as in the present study, reported that risk of breast cancer was reduced by 18% by walking for 1.25 to 2.5 h/wk (22). The association between physical activity and breast cancer, unlike what we report for the relationship between physical activity and breast density, remains significant when adjusted for measures of anthropometry such as BMI. Physical activity, therefore, does seem to have an independent effect that leads to a decrease in risk of breast cancer.

Thus, our results suggest that a mechanism other than breast density explains the association between physical activity and breast cancer risk. Our findings and one previous study (26) both found that associations between physical activity and breast density were attenuated after adjustment for BMI, suggesting that the effects of physical activity on the characteristics of the breast may be mediated through changes in weight. Specifically, we observed significant age-adjusted associations between physical activity and the sizes of the total breast area and non-dense area; however, these associations were no longer significant when adjusted for BMI. In contrast, physical activity was not associated with the size of the dense area both before and after adjustment for BMI. There was a suggestion that mild physical activity may be associated with dense area and percent density among well controls, but this finding is likely due to chance for the previously stated reasons. Together, these data suggest that whereas physical activity may not affect dense breast tissue (and hence not reduce mammographic breast density), physical activity may exert its protective effect on breast cancer through affecting the fatty tissue of the breast. Indeed, physical activity has been shown to result in reduced metabolically active fat mass (37), decreased levels of insulin and glucose (37), increased levels of insulin-like growth factor binding protein-3 (37), decreased levels of sex hormones such as estradiol (37), and decreased markers of systemic inflammation (38-41), all of which may be associated with reduced risk of breast cancer (42-45). Despite intriguing evidence for each of these pathways, however, the exact mechanism by which physical activity reduces the risk of breast cancer, but seemingly not mammographic density, remains elusive.

There are a number of limitations of the present study that must be considered. First, a significant limitation of this and other previous studies is the cross-sectional nature of the analysis. A second limitation results from the physical activity measure used, which included only recreational physical activity. This method neglected to capture occupational and household activities, which may be related to breast cancer and are likely to be important sources of physical activity for women (23, 46), potentially introducing nondifferential misclassification bias and biasing results toward the null. Although we used a previously tested, reliable questionnaire

Table 7. Multivariable associations between recreational physical activity variables and breast density variables, well controls (n = 504)

Recreational physical activity variable	Adjusted for age		Adjusted for age and BMI		Fully adjusted model*	
	β	P	β	P	β	P
Dense area						
Cumulative exercise, MET-h/wk	0.027	0.71	0.023	0.76	0.028	0.71
Mild exercise, h/wk	1.44	0.06	1.42	0.07	1.59	0.04
Moderate or strenuous exercise, h/wk	0.14	0.82	0.11	0.86	0.11	0.85
Non-dense area						
Cumulative exercise, MET-h/wk	−0.99	<0.0001	−0.22	0.19	−0.20	0.24
Mild exercise, h/wk	−5.42	0.01	−1.97	0.24	−2.04	0.22
Moderate or strenuous exercise, h/wk	−5.55	0.0006	−1.29	0.32	−1.11	0.41
Total breast area						
Cumulative exercise, MET-h/wk	−0.96	<0.0001	−0.19	0.25	−0.20	0.23
Mild exercise, h/wk	−3.98	0.06	−0.55	0.75	−0.39	0.82
Moderate or strenuous exercise, h/wk	−5.41	0.0009	−1.19	0.36	−1.28	0.35
% Density						
Cumulative exercise, MET-h/wk	0.18	0.0004	0.041	0.40	0.059	0.21
Mild exercise, h/wk	1.64	0.003	1.05	0.03	1.33	0.005
Moderate or strenuous exercise, h/wk	0.97	0.02	0.19	0.62	0.26	0.48

NOTE: Estimated coefficients are for a 1-unit increase in the continuous recreational physical activity variable (MET-h/wk). P from t test of coefficients.
*Variables and n included in fully adjusted model differed for each density outcome. Dense area: age, BMI, number live births, number of breast biopsies, interval between mammogram and questionnaire (n = 502). Non-dense area: age, BMI, race, smoking status, number of breast biopsies, quality of film, alcohol intake in year prior to enrollment (n = 494). Total breast area: age, BMI, history of breast-feeding, quality of film, alcohol use in year before enrollment (n = 495). % Density: age, BMI, race, age at first pregnancy >6 mo, history of breast-feeding, number of breast biopsies, quality of film, interval between mammogram and questionnaire (n = 499).

for measuring physical activity, it should be noted that the reliability of these recreational physical activity questions was tested in a somewhat different population of women, a random sample of postmenopausal women participating in the WHI. In the WHI, the test-retest reliability (weighted κ) for the physical activity variables ranged from 0.53 to 0.72, and the intraclass correlation coefficient for total physical activity expenditure in MET was 0.77 (22, 31). Hence, whereas this measurement tool was reasonably reproducible in the WHI, the reliability of this instrument may not extend to the premenopausal and postmenopausal women participating in MAMS. Again, inadequate classification of recreational physical activity could in part explain the observed null results.

This study is strengthened by its large sample size and, to our knowledge, is the largest study to date to have characterized the relationships between physical activity and the dense, non-dense, and total areas of the breast in addition to percent breast density. As percent density is highly related to body weight, it is important to consider other mammographic characteristics that are less confounded by body weight, such as the dense breast area, in studies examining mammographic density (47). In addition, we examined these relationships in cancer-free women who received screening mammograms or benign breast biopsies, a clinically meaningful subgroup of the population at risk for breast cancer in whom breast density has not previously been well studied with respect to physical activity. Nevertheless, because the MAMS population consists of this unique, nonrandom sample of cancer-free women, participants may not be entirely representative of the general population from which they were sampled. On average, MAMS women were more likely to be White and were better educated than same-aged women residing in Allegheny County, PA in 2005: 94% versus 87%[3] were White (48), and 77% versus 61% reported completing post-secondary education, respectively (49). In addition, MAMS women seem to be healthier than the population from which they were recruited. MAMS women were less likely to be current smokers: 9% versus 16% (49). In addition, MAMS women were more likely to participate in physical activity (87% reporting any recreational physical activity in MAMS versus 77% of same-aged women reporting any leisure-time physical activity in 2005 in Allegheny County; ref. 49) and reported a greater prevalence of moderate or vigorous physical activity (54% versus 49%; ref. 49). When comparing MAMS women with 2005 Allegheny County residents of the same age who also reported having a mammogram within the past 12 months, these differences were still evident, likely reflecting a ''healthy volunteer'' effect. Hence, generalizability of results to other populations may be limited.

This study adds to the existing body of literature showing no association between recreational physical activity and mammographic breast density among cancer-free women. As the strong relationship between breast density and BMI may obscure this association, future research might explore the influence of physical activity on mammographic density over time, using serial mammograms. Such longitudinal studies could help to explain how changes in levels of physical activity relate to changes in the mammographic characteristics of the breast and may be more sensitive for detecting an association, if one does exist.

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Recreational Physical Activity and Mammographic Breast Density Characteristics

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