



Original Contribution

Physical Activity and Change in Mammographic Density

The Study of Women's Health Across the Nation

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One potential mechanism by which physical activity may protect against breast cancer is by decreasing mammographic density. Percent mammographic density, the proportion of dense breast tissue area to total breast area, declines with age and is a strong risk factor for breast cancer. The authors hypothesized that women who were more physically active would have a greater decline in percent mammographic density with age, compared with less physically active women. The authors tested this hypothesis using longitudinal data (1996–2004) from 722 participants in the Study of Women's Health Across the Nation (SWAN), a multiethnic cohort of women who were pre- and early perimenopausal at baseline, with multivariable, repeated-measures linear regression analyses. During an average of 5.6 years, the mean annual decline in percent mammographic density was 1.1% (standard deviation = 0.1). A 1-unit increase in total physical activity score was associated with a weaker annual decline in percent mammographic density by 0.09% (standard error = 0.03; $P = 0.01$). Physical activity was inversely associated with the change in nondense breast area ($P < 0.01$) and not associated with the change in dense breast area ($P = 0.17$). Study results do not support the hypothesis that physical activity reduces breast cancer through a mechanism that includes reduced mammographic density.

breast neoplasms; exercise; longitudinal studies; mammography; physical fitness; risk factors

Abbreviations: KPAS, Kaiser Physical Activity Survey; SD, standard deviation; SWAN, Study of Women's Health Across the Nation.

The proportion of radiologically dense breast tissue area to total breast tissue area, or percent mammographic density, may be a biologic marker of cumulative exposure to factors, such as hormones and growth factors, that affect the rate of aging of breast tissue (1). The rate of breast tissue aging is related to exposures that affect the proliferation of breast cells and, in turn, the potential for the accumulation of genetic damage (1). Identifying lifestyle factors associated with decreasing mammographic density, independent of age, may have important implications for breast cancer prevention because these factors may reflect a lower cumulative exposure to factors that decrease breast tissue aging.

Physical activity is one of the few modifiable factors associated with a modest reduction in breast cancer risk,

independent of its effects on body mass (2–4). Similar risk reductions have been found in diverse populations (4). The greatest risk reductions were found for recreational activity, compared with household or occupational activity (4).

One mechanism by which physical activity may exert a protective effect on breast cancer risk is through reducing cumulative exposure to endogenous reproductive hormones (4) and, thereby, reducing breast cell proliferation (5) and possibly the rate of breast tissue aging. This mechanism would be supported by an inverse association between physical activity and mammographic density. Results from cross-sectional analyses of current physical activity and percent mammographic density have been inconsistent. Studies

have reported a weak inverse relation (6, 7) or no evidence of an association (8–11).

Mammographic density is not a static trait but rather declines by an estimated 0.4%–1.9% annually in premenopausal women (12–14), with the greatest decrease occurring during the menopausal transition (12, 15). Identifying factors that influence the rate of change in mammographic density, especially during the critical time period when the reduction in mammographic density is the greatest, may provide important information not available from studies examining factors associated with mammographic density at one point in time. In epidemiologic studies, the rate of change in mammographic density may be modified by breast cancer risk factors. For example, a slower decline in percent mammographic density has been observed with current hormone replacement therapy use and higher body mass index (14, 15).

We evaluated whether change in mammographic density was modified by physical activity in the Study of Women's Health Across the Nation (SWAN), a community-based cohort of Chinese, Japanese, African-American, and non-Hispanic white women who were followed during the menopausal transition. Specifically, we hypothesized that women who were more physically active would have a greater decline in percent mammographic density, compared with those who were less physically active.

MATERIALS AND METHODS

Study population

SWAN is a multiethnic, longitudinal study of the menopausal transition (16). Briefly, from 1996 to 1997, women were identified from defined sampling frames at 7 clinical sites throughout the United States. At baseline, eligible women were between 42 and 52 years of age and reported having had a menstrual period and no use of hormone replacement therapy within the 3 months prior to recruitment. Participants had a variety of measurements taken and completed interviews and questionnaires at baseline and at annual follow-up visits.

The SWAN mammographic density ancillary study was conducted among SWAN participants enrolled at 3 of the 7 study sites: University of California, Davis/Kaiser, Oakland, California; University of California, Los Angeles, California; and University of Pittsburgh, Pittsburgh, Pennsylvania. Of the women available at the fifth and sixth annual follow-up visits, 1,005 women (81%) agreed to participate and had at least 1 eligible mammogram for density assessment. For analyses presented here, women were excluded if they were not pre- or early perimenopausal (defined below) at their index mammogram ($n = 210$), had only one mammogram ($n = 65$), or were missing breast density measures ($n = 8$). Women who reported hormone replacement therapy use at a follow-up visit ($n = 207$) were included in this study. A total of 722 women constituted the study population. The study protocols for both the core SWAN study and the mammographic density ancillary study were approved by the institutional review boards of the participating institutions,

and all women provided signed, written informed consent for participation in the studies.

Mammographic density

Eligible mammograms were taken as part of routine medical care from 2 years prior to the baseline SWAN visit through 2 years after the sixth annual follow-up visit. We defined the "index" mammogram as the earliest available mammogram within 2 years of the SWAN visit when physical activity was assessed. The SWAN visit closest in time to the index mammogram date was the baseline for the majority of women (86%). The average lag between the index mammogram and the SWAN visit was 0.6 years (standard deviation (SD) = 0.5; range, 0–2 years). Mammographic density measurements from 3,378 films were available for analyses. We excluded 9 films, because they were taken within 4 months of a subsequent mammogram and were suspected to be for diagnostic purposes. The average number of mammograms per woman was 5.4 (SD = 1.8; range, 2–10 mammograms), and the average time between subsequent mammograms was 1.7 years (SD = 1.0; range, 0.4–9.1 years). The average follow-up from the index to last mammogram was 5.6 years (SD = 1.7; range, 0.9–9.1 years).

Mammograms were sent periodically in batches to Martine Salane, an established expert in the techniques of measuring mammographic density (17–19). Unknown to Martine Salane, 10% of the films for this study were sent for rereview. The initial and repeat readings had excellent concordance (within-person Spearman correlation coefficient of percent mammographic density = 0.96; mean difference in percent mammographic density assessments = 2.2%). Quantitative assessment was obtained by measuring the total area of the breast and the area of dense breast tissue with a compensating polar planimeter (Los Angeles Scientific Instrument Co., Inc. (LASICO), Los Angeles, California) on the craniocaudal view of the right breast.

Physical activity measurements

Physical activity was assessed at baseline and at annual follow-up visits 3, 5, and 6 by using the Kaiser Physical Activity Survey (KPAS), an adaptation (20) of the Baecke physical activity questionnaire (21). The self-administered survey assessed physical activity in several different domains over the past year; the 1-month test-retest reliability of the KPAS has been found to be high (intraclass correlations: sports/exercise $r = 0.84$, daily routine $r = 0.82$, household/caregiving $r = 0.81$; $P < 0.001$ for all) and has demonstrated validity against activity records, accelerometer recordings, and maximal oxygen consumption (22). The KPAS consisted of a series of questions with primarily Likert-type response categories that ask about physical activity in mutually exclusive domains of sports/exercise, household/caregiving, occupational, and daily routine. The household/caregiving questions asked about the frequency of various activities. The sports/exercise index was based primarily on questions that ask about frequency, duration, perceived physical exertion, and an assigned intensity value.

Daily routine was defined as the frequency of walking or biking for transportation and hours of television viewing, which were reverse scored. Physical activity summary variables, expressed as domain-specific indices, were derived by summing up the response values and dividing by the total of nonmissing items. The values ranged from 1 (lowest) to 5 (highest) and represented the relative ranking of individuals by domain-specific physical activity level. Total physical activity was the sum of all the indices. Occupational physical activity was not included in analyses, because 16% of the women self-reported not working outside of the home.

Covariates

Covariate data used from the baseline visit included the following: self-reported race/ethnicity, education, age at menarche, parity, age when first child was born, family history of breast cancer, and prior hormone use (e.g., birth control pills and/or injections, estrogen and/or progestin pills, injections, and/or patches). Perceived health status was based on baseline responses because of complete data. Time-dependent covariate data, such as body mass index, menopausal status, annual household income, and smoking history, were obtained from the SWAN visit closest in time to the mammogram date. Weight and height were measured with calibrated electronic or balance-beam scales and stadiometer at each visit and were used to calculate body mass index (weight (kg)/height (m)²). Menopausal status was based on response to questions on the date of last menstrual bleeding, changes in regularity of bleeding, hormone replacement therapy use, and hysterectomy and oophorectomy at each visit as follows: 1) premenopause, a menstrual period within the past 3 months with no change in regularity; 2) early perimenopause, a menstrual period within the past 3 months but with a change in cycle lengths; 3) late perimenopause, no menstrual bleeding for 3–11 months; 4) postmenopause, no menstrual bleeding for at least 12 months; 5) surgical menopause, hysterectomy and/or bilateral oophorectomy; and 6) undetermined, use of hormone replacement therapy prior to 12 months of amenorrhea. Age was calculated on the basis of the date of the index mammogram.

Statistical analyses

The primary goal of these analyses was to assess the presence of an interaction between physical activity and age-related change in percent mammographic density. The secondary outcomes, area of dense breast tissue and area of nondense breast tissue, were log transformed to normalize their distributions. Statistical computing was conducted by using SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina).

Within-woman change for time-dependent variables was calculated as the difference between the value at subsequent assessment and the index value collected at the SWAN visit closest to the index mammogram. For menopausal status, the change variable was defined as 1) no change in menopausal status, 2) premenopausal to early perimenopausal, 3) premenopausal to late perimenopausal, 4) early perimen-

opausal to late perimenopausal, 5) premenopausal to naturally postmenopausal, 6) early perimenopausal to naturally postmenopausal, and 7) became postmenopausal due to surgery or hormone replacement therapy use.

Mixed-effects linear models were used to estimate the association between physical activity and average annual change in percent mammographic density. Separate models were built for each physical activity index with time modeled as years since the index mammogram. The primary effects of interest were the interactions of physical activity measured at the index mammogram and time and the interactions of change in physical activity and time. These models account for the correlation of repeated observations within women and unbalanced time between measures (23).

Model building began with the physical activity measures. Other covariates were then added to the models. We planned to adjust for age (continuous), body mass index (continuous), parity (0, 1–2, ≥ 3), menopausal status (premenopausal, early perimenopausal), and prior hormone use (yes/no), because these factors were associated with mammographic density in previous analyses of this cohort (24). Other covariates remained in the model if the beta coefficient value for physical activity changed by at least 10%. The following covariates were included in all adjusted models: race/ethnicity–study site (non-Hispanic white–Oakland, Chinese–Oakland, non-Hispanic white–Los Angeles, Japanese–Los Angeles, non-Hispanic white–Pittsburgh, African American–Pittsburgh) and smoking (never, former, current). Change in menopausal status and change in body mass index were included in the models as interactions with time. Interactions between time and covariates (e.g., race/ethnicity–study site and body mass index) that had $P \leq 0.05$ remained in the model. A combined variable race/ethnicity–study site was created because, in addition to non-Hispanic whites, each study site recruited women from a specific racial/ethnic group, Japanese (Los Angeles), African American (Pittsburgh), and Chinese (Oakland).

Secondary analyses included examination of interactions, for example, whether the association between percent mammographic density and physical activity varied by age (<45, 45–49, ≥ 50 years), body mass index (<25, ≥ 25 kg/m²), race/ethnicity–study site, menopausal status (no change, became early/late perimenopausal, became naturally postmenopausal, hormone replacement therapy use during any follow-up visit), and smoking status (ever/never) using stratified analyses and the inclusion of 3-way interaction terms. Statistically significant interactions from the adjusted model were assessed with $P \leq 0.05$.

RESULTS

Our cohort of 722 women were approximately 50% non-Hispanic white and had a median age of 46.3 years (interquartile range = 4.0) and a body mass index of 24.1 kg/m² (interquartile range = 6.4) at the time of the index mammogram. A majority were parous (82%), premenopausal at the index mammogram (53%), and never smokers (69%). Women in the highest tertile of physical activity were more likely to be thinner, to be non-Hispanic white, or to have

Table 1. Study Population Characteristics by Total Physical Activity Level, Study of Women's Health Across the Nation, 1996–2004

Characteristics ^a	Total Physical Activity Level ^b			P Value ^c
	Low (0.0–7.0) (n = 225)	Medium (7.1–8.5) (n = 244)	High (8.6–15) (n = 253)	
Age, %				
40–44 years	27	30	31	
45–49 years	56	56	52	
50–55 years	17	14	17	0.70
Body mass index, %				
<18.5 kg/m ²	2	1	2	
18.5–24.9 kg/m ²	52	55	64	
25.0–29.9 kg/m ²	24	25	23	
≥30 kg/m ²	23	19	10	0.01
Race/ethnicity, %				
Non-Hispanic whites	41	46	60	
African American	7	7	5	
Chinese	31	24	17	
Japanese	20	23	19	<0.01
Parity, %				
Nulliparous	20	19	16	
1–2	57	61	57	
≥3	23	19	27	0.27
Menopausal status, %				
Premenopausal	51	51	57	
Early perimenopausal	49	49	43	0.36
Education, %				
High school or less	20	20	9	
Some college	31	30	26	
College or more	49	50	64	<0.01
Smoking status, %				
Never	71	72	63	
Former	20	21	27	
Current	9	8	10	0.20

Abbreviation: SWAN, Study of Women's Health Across the Nation.

^a Menopausal status and body mass index were based on data from the SWAN visit closest to the index mammogram. Age was based on the date of the index mammogram. Other variables were from the baseline SWAN visit.

^b Cutoffs represent tertiles on a 1–15 scale based on the distribution among all women. Percentages may not add to 100, because of rounding. There were missing values for parity ($n = 1$) and smoking status ($n = 1$).

^c P value from χ^2 test.

more education, compared with women in the lowest physical activity tertile (Table 1).

For the index mammogram, percent mammographic density was negatively correlated with increasing age, increasing body mass index, and early perimenopause (Table 2), as expected on the basis of previous studies.

Results of univariate analyses indicated that higher levels of total physical activity were associated with higher mean percent mammographic density for the index mammogram (Table 2). The strongest positive trend was observed for the sports/exercise physical activity index. Overall, the percent mammographic density declined an average of 1.1% per year. The annual decline in percent mammographic density varied by race/ethnicity and body mass index, but it did not vary by tertile of physical activity (total, sports/exercise, daily routine, or household/caregiving) or menopausal status for the index mammogram (Table 2). A greater annual decline in percent mammographic density was observed for women who naturally transitioned from premenopause/early perimenopause to postmenopause and for women who reported hormone replacement therapy use at any follow-up visit compared with women who stayed either premenopausal or early perimenopausal (Table 2).

Similar longitudinal trends were observed in separate mixed-effect regression models for each physical activity index with percent mammographic density over time (Table 3). Physical activity modified the annual change in percent mammographic density in unadjusted models, with higher levels of physical activity associated with a slower decline (e.g., $\beta > 0$) in percent mammographic density as shown in model 1 (Table 3). Adjustment for body mass index strengthened the relation among total activity, sports/exercise, and daily routine and change in mammographic density as shown in model 2 (Table 3). After adjustment for body mass index and other covariates in model 3 (Table 3), a 1-unit increase in total physical activity reduced the decline in percent mammographic density by 0.09 percentage points per year or 0.5 percentage points over 6 years. Similarly, a 1-point increase in sports/exercise and daily routine reduced the annual decline in percent mammographic density by 0.12 points and 0.15 points, respectively (Table 3). The association of longitudinal change in percent mammographic density with sports/exercise, daily routine, or household/caregiving indices did not differ by body mass index, age, race/ethnicity, smoking status, or change in menopausal status (data not shown). A total of 127 women (18% of the analytical cohort) had a child within the past 10 years of their index mammogram. The main findings for physical activity and percent mammographic density were similar when these women were excluded from analyses or when analyses were limited to mammographic data collected prior to report of first hormone replacement therapy use (data not shown).

During follow-up, a small proportion of women changed their activity levels (e.g., 11% decreased and 22% increased by at least 1 sports/exercise index score and 13% decreased and 10% increased by at least 1 household index score when the physical activity assessment closest to the index mammogram was compared with the assessment closest to the last mammogram). We compared change in each subsequent physical activity assessment from the index mammogram and observed small, statistically significant mean changes for the individual physical activity domains of sports/exercise (mean change from baseline = 0.2, SD = 1.0; $P < 0.01$) and household/caregiving indices (mean change

Table 2. Univariate Analyses of Measures of Percent Mammographic Density and Change in Percent Mammographic Density by Study Population Characteristics and Physical Activity Level, Study of Women's Health Across the Nation, 1996–2004

Characteristics ^a	No.	%	Percent Density ^b		Annual Change of Percent Density ^c	
			Mean (SD)	P Value ^d	Mean (SD)	P Value ^d
All women	722	100	44.5 (19.9)		–1.1 (2.2)	
Age						
40–44 years	212	29	47.5 (21.4)		–1.0 (1.6)	
45–49 years	396	55	43.7 (19.2)		–1.1 (2.3)	
50–55 years	114	16	41.9 (19.0)	0.03	–1.5 (2.6)	0.07
Race/ethnicity						
Non-Hispanic whites	357	49	42.0 (20.8)		–1.3 (1.9)	
African American	44	6	34.5 (21.5)		–0.2 (2.9)	
Chinese	170	24	51.1 (18.3)		–1.1 (1.9)	
Japanese	151	21	45.8 (16.4)	0.01	–0.9 (2.7)	0.01
Body mass index						
<25.0 kg/m ²	426	59	52.0 (17.1)		–1.4 (2.1)	
25.0–29.9 kg/m ²	172	24	41.3 (16.6)		–0.9 (2.4)	
≥30 kg/m ²	124	17	23.2 (16.3)	<0.001	–0.5 (2.2)	<0.001
Total physical activity						
<7.1	225	31	42.7 (21.2)		–1.1 (2.1)	
7.1–8.5	244	34	44.9 (19.7)		–1.2 (2.1)	
>8.5	253	35	45.7 (18.9)	0.23	–1.0 (2.4)	0.51
Physical activity domains						
Sports/exercise						
<2.5	250	35	43.0 (21.0)		–1.2 (2.0)	
2.5–3.5	262	36	43.7 (20.0)		–0.9 (2.3)	
>3.5	210	29	47.3 (18.3)	0.05	–1.2 (2.4)	0.21

Table continues

from baseline = -0.2 , SD = 0.8; $P < 0.01$) during follow-up. These small within-woman changes did not influence the decline in percent mammographic density: $\beta = -0.03$, SD = 0.04; $P = 0.50$ for sports/exercise; $\beta = 0.02$, standard error = 0.06; $P = 0.77$ for daily routine; and $\beta = -0.01$, SD = 0.06; $P = 0.82$ for household/caregiving.

Next, we evaluated the association between physical activity and change in dense, nondense, and total breast area (Table 4). Dense area decreased over the study period (mean = -0.7 cm²/year, SD = 3.1), and nondense and total area of the breast increased (mean = 2.1 cm²/year, SD = 5.5 for nondense area and mean = 1.4 cm² per year, SD = 5.3 for total area). Type of physical activity (total, sports/exercise, daily routine, or household/caregiving) did not modify the decline in dense area over time. However, women who were more physically active had a slower increase in nondense area, compared with less physically active women. For example, a one-unit increase in total physical activity was associated with a statistically significant slower increase of nondense area by 0.3% per year (Table 4). Total physical activity and daily routine were statistically significantly associated with

a slower increase in both nondense breast area and total breast area.

DISCUSSION

Using data from a prospective cohort of midlife women, we found that higher levels of the specific domains of sports/exercise and daily routine physical activity were associated with a slower decline in percent mammographic density over a mean follow-up time of 5.6 years, compared with lower levels of physical activity. On average, women experienced an annual 1.1% decline in percent mammographic density during follow-up, consistent with prior data on the age-related decline in premenopausal percent mammographic density (12, 14). In comparison, women with a 1-unit higher level of sports/exercise activity had an annual decline of 1.0 percentage point. We observed that this small relative decline was attributed to a small decline in the annual increase of nondense breast area.

Our findings do not support the notion that physical activity increases the age-related decline in percent

Table 2. Continued

Characteristics ^a	No.	%	Percent Density ^b		Annual Change of Percent Density ^c	
			Mean (SD)	P Value ^d	Mean (SD)	P Value ^d
Daily routine						
<2.5	315	44	42.0 (19.9)		-1.1 (2.1)	
2.5	206	28	47.1 (19.9)		-0.9 (2.5)	
>2.5	201	28	45.8 (19.6)	0.01	-1.3 (1.9)	0.13
Household/caregiving						
<2.1	287	40	45.7 (21.0)		-1.2 (2.1)	
2.1–3.5	283	39	45.2 (19.6)		-1.1 (2.7)	
>3.5	152	21	43.0 (18.9)	0.25	-1.0 (2.5)	0.54
Menopausal status						
At index mammogram						
Premenopausal	382	53	46.6 (19.2)		-1.2 (1.9)	
Early perimenopausal	340	47	42.2 (20.5)	<0.01	-1.0 (2.5)	0.18
At last mammogram ^e						
Stayed premenopausal or early perimenopausal	119	16	46.0 (20.9)		-0.5 (3.0)	
Became early perimenopausal	121	17	46.0 (19.2)		-0.6 (1.9)	
Became late perimenopausal	66	9	38.7 (19.7)		-1.1 (2.6)	
Became postmenopausal	185	26	45.9 (20.3)		-1.6 (1.7)	
Hormone therapy	207	29	45.9 (20.3)		-1.3 (2.1)	
Surgical menopause	24	3	44.7 (19.9)	0.11	-1.7 (1.5)	<0.001

Abbreviations: SD, standard deviation; SWAN, Study of Women's Health Across the Nation.

^a Age was based on the date of the index mammogram. Menopausal status, body mass index, and physical activity were based on data from the SWAN visit closest to the index mammogram. Physical activity was measured on a 1–15 scale for total and a 1–5 scale for activity domains; cutoffs represent tertiles of the distribution for all women.

^b Included density information from the index mammogram (refer to text for details).

^c Within-woman change in percent density from index to her last mammogram divided by years of follow-up time.

^d P value from analysis of variance.

^e Current use of menopausal hormone therapy at a follow-up visit; surgical menopause included hysterectomy/oophorectomy.

mammographic density. This finding is consistent with the few longitudinal studies available of physical activity and change in mammographic density (25, 26). In both prior studies, evaluating whether physical activity modified the change in mammographic density over time was not the primary aim, so we cannot directly compare our findings with theirs. In the first study, conducted in a small sample of Australian women ($n = 129$) who had undergone the menopausal transition, the frequency of engaging in exercise for fitness or recreation was not associated with change in percent mammographic density or dense breast area (25). Similar to our findings, the second study, conducted among participants in the Women's Health Initiative randomized trial ($n = 413$), found no association between change in physical activity, assessed as a covariate in metabolic equivalent hours/week, and change in percent mammographic density (26).

Physical activity is one of the few modifiable risk factors for breast cancer. When compared with inactivity, 2–4 hours

per week of moderate-to-vigorous exercise reduces risk by an average of 30%–40% (2). In our previous cross-sectional analyses of physical activity and mammographic density in SWAN, we reported weak inverse associations between the highest and the lowest category for sports/exercise, household/child care, and daily living domains with both percent mammographic density and dense breast area, although none of the associations was statistically significant (7). Our previous findings supported those from other cross-sectional studies, suggesting that physical activity was not a major factor associated with percent mammographic density (8–11, 27). As presented here, our longitudinal findings lend further support for a hypothesis that mammographic density is not a likely intermediate between physical activity and breast cancer. Contrary to our hypothesis, more intense physical activity was associated with a slower, rather than a faster, decline in percent mammographic density. A faster decline in mammographic density may be associated with lower breast cancer risk (28).

Table 3. Unadjusted and Adjusted Longitudinal Analyses for Change in Percent Mammographic Density^a by Physical Activity Indices, Study of Women's Health Across the Nation, 1996–2004

Physical Activity Index ^b	Model 1 ^c		Model 2 ^d		Model 3 ^e	
	β	95% Confidence Interval	β	95% Confidence Interval	β	95% Confidence Interval
Total activity	0.037	-0.027, 0.102	0.066	0.003, 0.130	0.087	0.024, 0.150
Sports/exercise	0.022	-0.083, 0.128	0.064	-0.040, 0.168	0.115	0.011, 0.219
Daily routine	0.045	-0.100, 0.190	0.128	-0.016, 0.272	0.149	0.009, 0.289
Household/caregiving	0.104	-0.036, 0.245	0.099	-0.038, 0.237	0.085	-0.051, 0.221

^a Values are maximum likelihood estimates of coefficients for modification to annual change in percent density and 95% confidence intervals from mixed-effects regression models.

^b One unit change in index measured on a 1–15 scale for total activity and a 1–5 scale for individual domains.

^c Model 1 represents univariate models for each activity index.

^d Model 2 represents individual models for each activity index adjusted for body mass index.

^e Model 3 represents single models for each activity index adjusted for age, body mass index, menopausal status, race/ethnicity, study site, parity, past use of hormones (contraceptive and postmenopausal hormones), smoking, change in body mass index, and change in menopausal status.

The total physical activity level modified the observed increase in area of nondense breast tissue but not the observed decrease in area of dense breast tissue, supporting an interaction with change in percent mammographic density only through nondense tissue. Specifically, we observed that a 1-unit higher level in total physical activity was associated with a statistically significant slower annual increase of nondense area of 0.3% and a nonstatistically significant slower annual decline in dense area by 0.2%. Our data support the hypothesis that physical activity may reduce breast cancer risk via a different mechanism than through an effect that decreases dense breast tissue area.

A primary strength of our study was the prospective design with multiple measures of mammographic density that enabled us to account for within-woman variability, to

assess trends over time, and to account for time-dependent covariates. In addition, our investigation was conducted among a multiethnic cohort of women and, therefore, likely to be more generalizable to the US population than previous studies of primarily white women. Also, covariate data were collected in person by trained interviewers who followed a specified protocol (16), thus limiting misclassification of important confounders for mammographic density, such as weight and height for the calculation of body mass index.

Strengths related to the measurement of our main exposure and outcome included a detailed assessment of physical activity, which allowed for interpretation for specific domains that accounted for frequency, intensity, and duration of exposure. The KPAS indices have been validated against

Table 4. Adjusted Longitudinal Analyses of Measures of Mammographic Density (Natural Logarithm Scale)^a by Changes of Physical Activity Indices, Study of Women's Health Across the Nation, 1996–2004

Physical Activity Index ^b	Dense Area		Nondense Area		Total Area	
	β	95% Confidence Interval	β	95% Confidence Interval	β	95% Confidence Interval
Total activity	0.0019	-0.0009, 0.0046	-0.0030	-0.0049, -0.0011	-0.0014	-0.0025, -0.0003
Sports/exercise	0.0029	-0.0016, 0.0075	-0.0030	-0.0061, 0.0001	-0.0012	-0.0030, 0.0006
Daily routine	0.0017	-0.0045, 0.0078	-0.0060	-0.0101, -0.0018	-0.0030	-0.0054, -0.0006
Household/caregiving	0.0024	-0.0035, 0.0083	-0.0039	-0.0079, 0.0002	-0.0013	-0.0037, 0.0010

^a Values are maximum likelihood estimates of coefficients for modification to annual change in dependent variables (dense, nondense, and total area) and 95% confidence intervals from mixed-effects regression models. The dependent variables, originally measured on a centimeter-squared scale, were log transformed to normalize distribution. Single models for each mammographic density measure were adjusted for age, body mass index, menopausal status, race/ethnicity, study site, parity, past use of hormones (contraceptive and postmenopausal hormones), smoking, change in body mass index, and change in menopausal status.

^b One unit change in index measured on a 1–15 scale for total activity and a 1–5 scale for individual domains.

activity records, accelerometers, and aerobic capacity (22). In addition, mammographic density measurements were made by using a planimeter assessment by a single expert with high reproducibility and accuracy (18, 19).

Our study had several limitations. Our power to detect small differences between physical activity and mammographic density, if a difference truly existed, was limited because our sample included few women at both the low and high extremes of physical activity. Additionally, the sensitivity of the KPAS in measuring change in physical activity is unknown, which may account for only modest within-woman change in physical activity observed during follow-up. KPAS indices represent relative ranking of activity levels and do not enable the conversion to quantifiable measures of energy expenditure or comparison between indices. Using mammographic density as a marker for breast cancer susceptibility had several limitations, as some factors do not appear to influence risk by affecting mammographic density (e.g., body mass index).

In conclusion, we observed statistically significant positive interactions between specific physical activity domains, sports/exercise and daily routine, with the decline in percent mammographic density among a multiethnic cohort of mid-life women. The observed associations appear to be mediated through a negative interaction with an increase in nondense breast tissue and, therefore, do not support the hypothesis that physical activity reduces breast cancer through a mechanism that includes reduced mammographic density. Future longitudinal studies are still needed, however, that assess whether increasing physical activity is needed to observe a beneficial decrease in mammographic density.

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