

# Long-term Recreational Physical Activity and Risk of Invasive and In Situ Breast Cancer

## The California Teachers Study

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**Background:** Long-term physical activity may affect breast cancer risk. Few prospective studies have evaluated in situ or invasive breast cancer risk, or breast cancer receptor subtypes, in relation to long-term activity.

**Methods:** We examined the association between recreational physical activity and risk of invasive and in situ breast cancer in the California Teachers Study, a cohort of women established in 1995-1996. Of 110 599 women aged 20 to 79 years with no history of breast cancer followed up through December 31, 2002, 2649 were diagnosed as having incident invasive breast cancer and 593 were diagnosed as having in situ breast cancer. Information was collected at cohort entry on participation in strenuous and moderate recreational activities during successive periods from high school through the current age or age 54 years (if older at enrollment) and in the past 3 years. A summary measure of long-term activity up to

the current age, or age 54 years if older, was constructed for each woman.

**Results:** Invasive breast cancer risk was inversely associated with long-term strenuous activity ( $>5$  vs  $\leq 0.5$  h/wk per year: relative risk, 0.80; 95% confidence interval, 0.69-0.94;  $P$  trend = .02), as was in situ breast cancer risk ( $>5$  vs  $\leq 0.5$  h/wk per year: relative risk, 0.69; 95% confidence interval, 0.48-0.98;  $P$  trend = .04). Strenuous and moderate long-term activities were associated with reduced risk of ER-negative (strenuous:  $P$  trend = .003; moderate:  $P$  trend = .003) but not ER-positive (strenuous:  $P$  trend = .23; moderate:  $P$  trend = .53) invasive breast cancer.

**Conclusion:** These results support a protective role of strenuous long-term exercise activity against invasive and in situ breast cancer and suggest differing effects by hormone receptor status.

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**F**EW ESTABLISHED RISK FACTORS for breast cancer are easily modifiable. Current evidence supports a reduction in breast cancer risk with regular physical activity, although data are based largely on case-control studies.<sup>1</sup> Biological mechanisms proposed to explain the protective relationship include pathways related to endogenous hormones, metabolism, and immune function.<sup>2-4</sup> Physical activity can modify menstrual characteristics, delaying age at menarche<sup>5</sup> and reducing the number of ovulatory cycles,<sup>6</sup> thus contributing to a potential decrease in lifetime exposure to ovarian hormones etiologically related to breast cancer.<sup>7,8</sup> Physical activity may also decrease bioavailable ovarian steroid hormone levels by increasing circulating levels of sex hormone binding globulin, a protein that binds and presumably inactivates estradiol.<sup>2,3</sup> Results of studies<sup>3</sup> regarding the immunomodulatory effects of physical activity are incon-

sistent but may involve effects on the number of natural killer cells and other immune factors, with effects varying with the intensity of activity.<sup>3</sup> In addition, physical activity may regulate energy balance, thereby reducing overall weight gain and abdominal adiposity and improving insulin sensitivity,<sup>2,4</sup> all of which have been linked to breast cancer risk.

Questions remain regarding the amount and intensity of physical activity and the periods when activity provides the greatest breast cancer risk reduction. Little information exists on whether impact varies by tumor receptor status.<sup>9-12</sup> Furthermore, the relationship between physical activity and in situ breast cancer is not well understood, as few studies have evaluated in situ separately from invasive breast cancer.<sup>13,14</sup> To address these issues, we examined the relationship between recreational physical activity measures and invasive and in situ breast cancer among women in the large California Teachers Study cohort.

## STUDY POPULATION

Details of the California Teachers Study have been described previously.<sup>15</sup> Briefly, the California Teachers Study is a prospective study of 133 479 current and retired female California public school teachers and administrators who were active members of the California State Teachers Retirement System when the cohort was established in 1995.

Participants with newly diagnosed first primary invasive or in situ breast cancer were identified through annual linkages with the California Cancer Registry, which has 99% complete reporting for breast cancer.<sup>16</sup> Person-time of follow-up began with the date the baseline questionnaire was completed in 1995-1996 and ended with the first of the following: a breast cancer diagnosis (invasive or in situ), a permanent move outside of California (n=5329), death (n=2898), or December 31, 2002.

We excluded women from the analytic cohort, sequentially, if they had a previous or unknown history of breast cancer (n=6274), were not California residents at baseline (n=8867), were 80 years or older at baseline (n=5133), or had incomplete data on physical activity (n=738) or menarche or reproductive history (n=1868). Of the 110 599 women remaining, 2649 were diagnosed as having invasive breast cancer during follow-up. For analyses of in situ breast cancer, we excluded the 2649 women diagnosed as having invasive breast cancer because the diagnosis of invasive disease presumes that the patients have passed through the in situ disease stage undetected. We also excluded 916 women with unknown smoking status (n=543) or unknown history of breast biopsy (n=373). In the cohort of 107 034 women eligible for in situ breast cancer analyses, 593 were diagnosed as having in situ breast cancer during follow-up, including 55 with lobular carcinoma in situ. For analyses of invasive breast cancer, we censored women who developed in situ breast cancer on the dates of their diagnoses.

The University of Southern California institutional review board approved the use of human subject data in these analyses in accord with an assurance filed with and approved by the US Department of Health and Human Services.

## RECREATIONAL PHYSICAL ACTIVITY MEASURES

Participants provided information at baseline regarding their participation in moderate and strenuous recreational physical activities between high school and their current age or age 54 years if 55 years or older as well as recent activity. Participants were provided examples of moderate activities (eg, brisk walking, golf, and volleyball) and strenuous activities (eg, swimming laps, aerobics/calisthenics, running, and jogging) and reported their mean hours per week (none, 0.5, 1, 1.5, 2, 3, 4-6, 7-10, and  $\geq 11$  hours) and months per year (1-3, 4-6, 7-9, and 10-12 months) of participation at each level of activity during high school; from ages 18 to 24 years, 25 to 34 years, 35 to 44 years, and 45 to 54 years; and in the past 3 years. We created separate strenuous and moderate mean annual hours per week activity variables for each period by multiplying the hours per week by the portion of the year in which the woman engaged in the activity. We assigned the midpoint value of the categories in making these calculations, assigning a value of 12 for the category 11 h/wk or more.

Measures of long-term strenuous and long-term moderate physical activity were calculated for each participant by multiplying the average annual hours per week of activity during a period by the number of years the woman spent in that period, summing across all relevant periods, and dividing this cumulative

measure by the total number of years spent across all periods. The categories established for strenuous and moderate long-term activity measures were 0.50 or less, 0.51-2.00, 2.01-3.50, 3.51-5.00, and more than 5.00 annual hours per week.

## ASSESSMENT OF BREAST CANCER RISK FACTORS

We collected information on relevant breast cancer risk factors at baseline, including race/ethnicity, family history of breast cancer, age at menarche, reproductive history, menopausal status, use of hormone therapy (HT) and oral contraceptives, height, weight, diet, smoking history, alcohol consumption, mammography screening history, and breast biopsy history.<sup>15</sup> Quartiles of body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) were based on the distribution in the cohort. Women were considered premenopausal if they were having menstrual periods at baseline. Women whose menstrual periods stopped within 6 months of the baseline questionnaire were classified as perimenopausal. Women were postmenopausal if they reported that their periods had stopped more than 6 months earlier (natural menopause or both ovaries removed) or they were 56 years or older (whether or not they were currently taking HT) and were not considered premenopausal or perimenopausal. Younger women currently taking some form of HT for more than 1 year whose periods had not stopped and those who had a hysterectomy without bilateral oophorectomy were assigned unknown menopausal status.

## STATISTICAL ANALYSES

We used multivariable Cox proportional hazards regression<sup>17</sup> to estimate the association (relative risk [RR] and 95% confidence interval [CI]) between physical activity and breast cancer risk, conducting analyses separately for invasive and in situ breast cancer. In the Cox regression models, the time scale was defined by age at baseline (entry) and age at event or censoring (exit). We evaluated the relationship between the individual physical activity measures and invasive and in situ breast cancer risk using 2 models: an age-adjusted model and a multivariable model with adjustments for race (white, black, Asian, Hispanic, or other/unspecified), family history of breast cancer in a first-degree relative (yes, no, or unknown/adopted), HT/menopausal status (premenopausal, perimenopausal, postmenopausal/never used HT, postmenopausal/estrogen only therapy, postmenopausal/estrogen plus progesterone combined therapy, postmenopausal/estrogen alone and estrogen plus progesterone therapy, or unknown menopausal status/unknown HT use), BMI (<21.4, 21.4-23.6, 23.7-27.2,  $\geq 27.3$ , or unknown), history of smoking at least 100 cigarettes (never, current, past, or unknown), alcohol intake during the past year ( $\leq 15$  g/d,  $>15$  g/d, or unknown), screening mammogram in the past 2 years (yes, no, or unknown), and history of a breast biopsy (yes, no, or unknown). Invasive breast cancer models also included a combined age at first full-term pregnancy and parity variable (age 15-24 years/1-3 term pregnancies, age 15-24 years/ $\geq 4$  term pregnancies, age 25-29 years/1-3 term pregnancies, age 25-29 years/ $\geq 4$  term pregnancies, age  $\geq 30$  years/1-3 term pregnancies, age  $\geq 30$  years/ $\geq 4$  term pregnancies, nulliparous, or unknown if had term pregnancies). The multivariable in situ breast cancer models included a less detailed pregnancy history variable (<25, 25-29, 30-34,  $\geq 35$  years at first term pregnancy, nulliparous, or unknown) due to the smaller number of in situ breast cancer cases in the expanded pregnancy categories. We did not include total caloric intake in the multivariable models because this was unrelated to either invasive or in situ breast cancer risk.<sup>18</sup>

**Table 1. Baseline Characteristics in Relation to Long-term Strenuous Physical Activity in 110 599 Women Eligible for the Analysis of Invasive Breast Cancer\***

Characteristic	Annual Strenuous Long-term Activity, h/wk					Women With Characteristic
	≤0.50	0.51-2.00	2.01-3.50	3.51-5.00	>5.00	
Participants, No. (%)	31 919 (28.9)	35 906 (32.5)	19 923 (18.0)	10 879 (9.8)	11 972 (10.8)	
Age at baseline, mean ± SD, y						
All women <80 y	56.7 ± 12.1	56.2 ± 12.4	48.4 ± 12.4	47.1 ± 12.9	46.5 ± 13.5	51.4 ± 13.1
Women 50-79 y	62.6 ± 8.4	60.6 ± 8.1	60.1 ± 8.0	60.3 ± 8.1	61.1 ± 8.1	61.3 ± 8.3
Women <50 y	42.2 ± 6.4	40.8 ± 6.8	39.9 ± 6.9	38.8 ± 7.1	37.9 ± 7.1	40.2 ± 7.0
Race, %						
White	86.1	86.7	86.3	85.6	85.5	95 330 (86.2)
Black	3.0	2.8	2.5	2.4	2.5	3008 (2.7)
Hispanic	3.8	4.4	5.1	5.5	5.0	5000 (4.5)
Asian	4.6	3.7	3.3	3.1	2.9	4126 (3.7)
American Indian, other, or unspecified	2.6	2.5	2.9	3.4	4.1	3135 (2.8)
First-degree family history of breast cancer, %†	13.3	12.3	11.4	11.2	10.6	12 920 (12.1)
History of breast biopsy, %	18.1	15.5	14.3	13.5	12.5	17 092 (15.5)
Had mammogram within 2 y of joining cohort, %	83.1	75.9	69.9	65.1	60.3	81 982 (74.1)
Age at menarche >13 y, %	19.5	19.1	20.4	21.6	24.3	22 438 (20.3)
Nulliparous, %	22.3	24.4	28.1	32.9	37.8	29 380 (26.7)
Menopausal status, %						
Premenopausal	27.9	47.0	57.0	60.4	61.7	46 642 (46.2)
Perimenopausal	2.4	2.6	2.2	2.2	1.9	2364 (2.3)
Postmenopausal, no hormone use	16.9	10.9	8.8	8.7	9.7	12 031 (11.9)
Postmenopausal, only estrogen alone use	22.4	15.5	12.6	11.4	11.1	16 258 (16.1)
Postmenopausal, only estrogen plus progestin use	19.3	15.9	12.7	11.2	10.4	15 384 (15.2)
Postmenopausal, estrogen alone and estrogen plus progestin use	11.1	8.2	6.7	6.1	5.2	8314 (8.2)
BMI, mean ± SD‡	25.4 ± 5.5	25.1 ± 5.3	24.7 ± 5.0	24.3 ± 4.9	23.9 ± 4.6	24.9 ± 5.2
Caloric intake, mean ± SD, kcal/d‡	1513 ± 534	1580 ± 552	1605 ± 559	1628 ± 579	1676 ± 605	1580 ± 559
Smoking status, %‡						
Never	65.3	65.9	67.3	67.7	69.1	73 163 (66.5)
Current	5.3	5.2	5.0	4.9	5.5	5696 (5.2)
Past	29.4	29.0	27.7	27.4	25.4	31 176 (28.3)
Alcohol use, %‡						
Nondrinker	38.1	32.0	31.0	30.6	30.2	34 953 (33.2)
<15 g/d	45.8	51.5	52.5	52.4	51.7	52 744 (50.2)
≥15 g/d	16.1	16.5	16.6	17.0	18.0	17 462 (16.6)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

\*Covers the period from high school to entry into the cohort or to age 54 years if 55 years or older at cohort entry.

†Family history in at least 1 first-degree relative.

‡Patients with unknown values were excluded from the appropriate calculations.

Trend tests for each physical activity variable were performed by fitting the median value of exposure categories in the statistical models and determining whether the slope variable differed from zero (Wald test). We evaluated effect modification by age at baseline, HT use among postmenopausal women, first-degree family history of breast cancer, parity, and BMI using a 1-df likelihood ratio test for heterogeneity of 2 trends.<sup>19</sup>

We examined the association between physical activity and invasive breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status of the tumors using information recorded by the California Cancer Registry. We had 1452 ER-positive/PR-positive (ER+/PR+), 305 ER+/PR-negative (PR-), and 309 ER-negative (ER-)/PR- tumors and 1879 ER+ and 345 ER- tumors. Too few breast cancers were ER-/PR+ for meaningful analysis (n=30). We tested for heterogeneity of trends in risk using a 1-df  $\chi^2$  test.

To determine the appropriateness of the proportional hazards assumption inherent in the Cox model, we visually examined Kaplan-Meier survival curves, plotted scaled Schoenfeld residuals,<sup>20</sup> and assessed the correlation of the residuals with time in the study. We observed no violations of the proportionality assumption. Two-sided *P* values are reported for tests

for trend and for heterogeneity of trends. We did not adjust CIs or *P* values for multiple comparisons. All statistical analyses were performed using the SAS software program (SAS version 9.1; SAS Institute Inc, Cary, NC).

## RESULTS

The mean ± SD age of women diagnosed as having invasive breast cancer was 61.7 ± 10.6 years (range, 27-86 years) and of women diagnosed as having in situ breast cancer was 60.9 ± 10.4 years (range, 37-86 years). The mean length of follow-up was 6.6 years. The distribution of participant characteristics for several breast cancer risk factors is given in **Table 1** across categories of long-term strenuous physical activity. Women reporting higher levels of strenuous activity were more likely to be younger (as reflected by age, menopausal status, and rates of mammography), to have later menarche, to be nulliparous, and to have a lower BMI, but only mod-

**Table 2. Relative Risk Estimates for the Association Between Physical Activity and Invasive Breast Cancer Risk in 110 599 Eligible Women**

Annual Physical Activity, h/wk	Observed Person-years	Breast Cancer Cases, No.	RR (95% CI)	
			Age Adjusted*	Multivariable Adjusted†
<b>Lifetime</b>				
<b>Strenuous</b>				
0-0.50	209 529	980	1 [Reference]	1 [Reference]
0.51-2.00	237 143	855	0.95 (0.86-1.04)	0.93 (0.85-1.02)
2.01-3.50	131 905	392	0.89 (0.79-1.00)	0.88 (0.78-0.99)
3.51-5.00	72 038	231	1.03 (0.89-1.19)	1.02 (0.88-1.18)
>5.00	78 888	191	0.81 (0.69-0.95)	0.80 (0.69-0.94)
<i>P</i> trend			.03	.02
<b>Moderate</b>				
0-0.50	150 052	594	1 [Reference]	1 [Reference]
0.51-2.00	263 588	961	1.06 (0.95-1.17)	1.02 (0.92-1.13)
2.01-3.50	150 037	537	1.05 (0.93-1.18)	1.02 (0.91-1.15)
3.51-5.00	83 936	287	1.02 (0.88-1.17)	0.99 (0.86-1.14)
>5.00	81 890	270	0.95 (0.82-1.10)	0.94 (0.81-1.08)
<i>P</i> trend			.37	.29
<b>Past 3 y</b>				
<b>Strenuous</b>				
0-0.50	489 278	1733	1 [Reference]	1 [Reference]
0.51-2.00	110 302	431	1.01 (0.91-1.12)	1.00 (0.90-1.11)
2.01-3.50	53 303	188	0.88 (0.76-1.03)	0.87 (0.75-1.01)
3.51-5.00	51 269	198	1.00 (0.86-1.16)	0.99 (0.86-1.15)
>5.00	25 350	99	0.98 (0.80-1.20)	0.99 (0.81-1.21)
<i>P</i> trend			.57	.56
<b>Moderate</b>				
0-0.50	346 838	990	1 [Reference]	1 [Reference]
0.51-2.00	172 436	727	1.06 (0.96-1.16)	1.03 (0.94-1.14)
2.01-3.50	82 319	360	1.04 (0.92-1.17)	1.02 (0.90-1.15)
3.51-5.00	82 732	352	0.96 (0.85-1.09)	0.94 (0.83-1.07)
>5.00	45 177	220	1.04 (0.90-1.21)	1.03 (0.88-1.19)
<i>P</i> trend			.97	.80

Abbreviations: CI, confidence interval; RR, relative risk.

\*Age (in months) is used as the time metric for the Cox proportional hazards models; models are stratified by age (in years).

†Adjusted for categories of race, family history of breast cancer, age at first full-term pregnancy and number of full-term pregnancies combined variable, hormone therapy and menopausal status combined variable, body mass index, smoking history, alcohol consumption, history of breast biopsy, and mammography screening.

est differences were observed across activity categories for other variables.

Age- and multivariable-adjusted risk estimates for the association of invasive breast cancer (**Table 2**) and in situ breast cancer (**Table 3**) with recreational physical activity did not differ substantially. Invasive breast cancer risk was reduced among women annually participating in more than 5 h/wk of strenuous activity relative to the least active women (RR, 0.80; 95% CI, 0.69-0.94; *P* trend=.02). Long-term moderate physical activity and strenuous and moderate activity in the past 3 years were not associated with invasive breast cancer. In situ breast cancer risk was also reduced among women in the highest vs lowest long-term strenuous physical activity category (RR, 0.69; 95% CI, 0.48-0.98; *P* trend=.04). We observed no statistically significant inverse trends in risk of in situ breast cancer with increasing levels of moderate or recent activity. Exclusion of the 55 patients with lobular carcinoma in situ did not alter these results (data not shown).

The RR estimates did not change for invasive or in situ breast cancer when we fit strenuous and moderate long-

**Table 3. Relative Risk Estimates for the Association Between Physical Activity and In Situ Breast Cancer Risk in 107 034 Eligible Women**

Annual Physical Activity, h/wk	Observed Person-years	Breast Cancer Cases, No.	RR (95% CI)	
			Age Adjusted*	Multivariable Adjusted†
<b>Lifetime</b>				
<b>Strenuous</b>				
0-0.50	204 179	215	1 [Reference]	1 [Reference]
0.51-2.00	232 279	202	0.98 (0.81-1.19)	0.96 (0.79-1.17)
2.01-3.50	129 378	89	0.88 (0.69-1.13)	0.86 (0.67-1.11)
3.51-5.00	70 652	50	0.97 (0.71-1.33)	0.95 (0.70-1.30)
>5.00	77 515	37	0.70 (0.49-0.99)	0.69 (0.48-0.98)
<i>P</i> trend			.052	.04
<b>Moderate</b>				
0-0.50	146 036	144	1 [Reference]	1 [Reference]
0.51-2.00	258 244	218	0.96 (0.78-1.19)	0.93 (0.75-1.15)
2.01-3.50	146 827	113	0.89 (0.69-1.14)	0.87 (0.68-1.12)
3.51-5.00	82 408	64	0.91 (0.68-1.22)	0.89 (0.66-1.20)
>5.00	80 487	54	0.78 (0.57-1.07)	0.78 (0.57-1.06)
<i>P</i> trend			.10	.11
<b>Past 3 y</b>				
<b>Strenuous</b>				
0-0.50	479 086	392	1 [Reference]	1 [Reference]
0.51-2.00	107 927	90	0.92 (0.73-1.16)	0.91 (0.72-1.14)
2.01-3.50	52 195	50	1.04 (0.77-1.39)	0.99 (0.74-1.33)
3.51-5.00	50 079	48	1.07 (0.80-1.45)	1.03 (0.76-1.40)
>5.00	24 717	13	0.58 (0.34-1.01)	0.57 (0.33-0.99)
<i>P</i> trend			.27	.17
<b>Moderate</b>				
0-0.50	339 880	235	1 [Reference]	1 [Reference]
0.51-2.00	168 618	145	0.89 (0.72-1.10)	0.86 (0.70-1.07)
2.01-3.50	80 536	82	1.02 (0.79-1.31)	0.99 (0.76-1.28)
3.51-5.00	80 861	92	1.10 (0.86-1.41)	1.05 (0.82-1.35)
>5.00	44 109	39	0.83 (0.59-1.17)	0.80 (0.57-1.14)
<i>P</i> trend			.81	.60

Abbreviations: CI, confidence interval; RR, relative risk.

\*Age (in months) is used as the time metric for the Cox proportional hazards models; models are stratified by age (in years).

†Adjusted for categories of race, family history of breast cancer, age at first full-term pregnancy hormone therapy and menopausal status combined variable, body mass index, smoking history, alcohol consumption, history of breast biopsy, and mammography screening.

term activity simultaneously in the same model (data not shown). We also observed no interaction between moderate and strenuous activity and no impact of moderate activity in the absence of strenuous activity (data not shown).

We evaluated the effects of strenuous and moderate recreational physical activity during different periods (data not shown). Risk patterns and risk estimates for the association between invasive and in situ breast cancer and strenuous physical activity performed at ages 25 to 34 years and 35 to 44 years were similar in magnitude to the estimates given in Tables 2 and 3; physical activity at ages 45 to 54 years was not associated with either invasive or in situ breast cancer. In situ but not invasive breast cancer was associated with strenuous activity during high school and at ages 18 to 24 years.

We observed significant decreases in invasive breast cancer risk with increasing levels of long-term strenuous recreational physical activity among younger women (*P* trend=.02), women with no first-degree family history of breast cancer (*P* trend=.01), women with a BMI less than 25 (*P* trend=.03), and parous women (*P* trend=.002), yet

**Table 4. Strenuous Long-term Physical Activity and Multivariable-Adjusted Relative Risk of Invasive Breast Cancer by First-Degree Family History of Breast Cancer, BMI, Parity, and Age\***

Variable	Breast Cancer Cases, No.	Annual Strenuous Long-term Physical Activity, h/wk†					P Trend	P Value for Homogeneity of Trends
		≤0.50	0.51-2.00	2.01-3.50	3.51-5.00	>5.00		
Family history								
No	2067	1 [Reference]	0.92 (0.83-1.02)	0.89 (0.78-1.02)	1.03 (0.88-1.22)	0.74 (0.62-0.89)	.01	.41
Yes	491	1 [Reference]	0.96 (0.78-1.19)	0.85 (0.64-1.13)	0.89 (0.62-1.28)	1.02 (0.73-1.43)	.72	
BMI								
<25.0	1455	1 [Reference]	0.97 (0.86-1.09)	0.95 (0.81-1.10)	1.02 (0.84-1.23)	0.74 (0.60-0.91)	.03	.81
≥25.0	1094	1 [Reference]	0.91 (0.80-1.04)	0.78 (0.65-0.94)	1.05 (0.84-1.31)	0.85 (0.67-1.09)	.12	
Parity								
Nulliparous	618	1 [Reference]	0.94 (0.77-1.15)	0.95 (0.74-1.21)	1.26 (0.96-1.65)	1.01 (0.77-1.33)	.43	.02
Parous	2016	1 [Reference]	0.93 (0.84-1.04)	0.86 (0.75-0.99)	0.94 (0.79-1.11)	0.73 (0.60-0.89)	.002	
Age, y								
<55	1062	1 [Reference]	0.87 (0.75-1.02)	0.83 (0.69-0.99)	1.00 (0.81-1.24)	0.68 (0.53-0.87)	.02	.25
≥55	1587	1 [Reference]	0.97 (0.86-1.09)	0.91 (0.77-1.06)	1.00 (0.82-1.22)	0.90 (0.74-1.10)	.27	

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

\*Adjusted for categories of race, family history of breast cancer, age at first full-term pregnancy and number of full-term pregnancies combined variable, hormone therapy and menopausal status combined variable, BMI, smoking history, alcohol consumption, history of breast biopsy, and mammography screening.

†Data are given as relative risk (95% confidence interval).

**Table 5. Long-term Physical Activity and Multivariable-Adjusted Relative Risk of Invasive Breast Cancer by Estrogen Receptor and Progesterone Receptor Status\***

Annual Long-term Physical Activity, h/wk	ER Positive (n = 1879)		ER Negative (n = 345)		RR (95% CI)		
	Breast Cancer Cases, No.	RR (95% CI)	Breast Cancer Cases, No.	RR (95% CI)	ER Positive/PR Positive (n = 1452)	ER Positive/PR Negative (n = 305)	ER Negative/PR Negative (n = 309)
Strenuous							
0-0.50	699	1 [Reference]	134	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
0.51-2.00	602	0.93 (0.83-1.04)	112	0.84 (0.65-1.09)	0.98 (0.86-1.11)	0.82 (0.62-1.07)	0.86 (0.66-1.12)
2.01-3.50	267	0.85 (0.74-0.99)	56	0.84 (0.61-1.15)	0.91 (0.77-1.07)	0.82 (0.57-1.16)	0.88 (0.63-1.22)
3.51-5.00	163	1.02 (0.86-1.21)	27	0.79 (0.52-1.20)	1.05 (0.86-1.28)	0.98 (0.64-1.50)	0.76 (0.48-1.19)
>5.00	148	0.89 (0.74-1.06)	16	0.45 (0.27-0.76)	0.94 (0.77-1.16)	0.75 (0.47-1.18)	0.35 (0.19-0.65)
P trend		.23		.003	.67	.31	.001
Moderate							
0-0.50	416	1 [Reference]	84	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
0.51-2.00	691	1.05 (0.93-1.19)	136	0.99 (0.75-1.31)	1.06 (0.93-1.22)	1.03 (0.75-1.40)	0.97 (0.73-1.30)
2.01-3.50	372	1.01 (0.88-1.17)	72	0.94 (0.68-1.29)	1.02 (0.87-1.20)	1.13 (0.80-1.59)	0.90 (0.64-1.26)
3.51-5.00	203	1.00 (0.85-1.19)	31	0.73 (0.48-1.10)	0.96 (0.79-1.17)	1.22 (0.82-1.81)	0.75 (0.49-1.15)
>5.00	197	0.98 (0.82-1.16)	22	0.53 (0.33-0.85)	1.02 (0.84-1.24)	0.95 (0.62-1.47)	0.50 (0.30-0.83)
P trend		.53		.003	.73	.86	.003

Abbreviations: CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; RR, relative risk.

\*Adjusted for categories of race, family history of breast cancer, age at first full-term pregnancy and number of full-term pregnancies combined variable, hormone therapy and menopausal status combined variable, body mass index, smoking history, alcohol consumption, history of breast biopsy, and mammography screening.

only the trends in risk for parous vs nulliparous women differed statistically ( $P=.02$ ) (**Table 4**). Reclassification of BMI to obese ( $>30$ ) vs nonobese women provided results similar to those given in Table 4 (data not shown). Among postmenopausal women, results for users of HT did not differ from those of nonusers (data not shown). Risk patterns were similar for in situ breast cancer, although for parity the test for homogeneity of trends was not statistically significant (data not shown).

Neither strenuous nor moderate long-term physical activity was associated with risk of ER+ invasive breast cancer (**Table 5**). Similar results were observed for ER+/

PR+ and ER+/PR- cancers. Participation in the highest categories of long-term physical activity was associated with a decreased risk of ER- invasive breast cancer, with risk reductions of 55% and 47% for strenuous and moderate long-term physical activity, respectively, relative to women who averaged 0.5 h/wk or less per year. The ER-/PR- cancer showed a similar risk pattern. All trends in risk for ER- breast cancer were statistically significant. These trends in risk for ER- breast cancer differed significantly from those for ER+ cancer (all  $P<.01$ ). We also assessed the association with ER status in premenopausal and postmenopausal women separately. Results

for postmenopausal women were similar to those given in Table 5. With the limited number of breast cancers in premenopausal women (79 ER- and 366 ER+), we did not detect differences in the trends in risk by ER status (data not shown). Analyses restricted to the 77% of women with a recent screening mammogram (within 2 years of baseline) differed minimally from those for the entire cohort in Tables 2, 3, 4, and 5 (data not shown).

## COMMENT

Results of case-control studies evaluating lifetime physical activity suggest an inverse association between physical activity and invasive breast cancer.<sup>1</sup> However, to our knowledge, this is the first prospective cohort study to assess the impact of accumulated long-term physical activity on breast cancer risk. Previous cohort studies<sup>1,14,21</sup> have included measures of current or recent recreational activity or activity at specific ages or time points and show reductions in risk ranging from 15% to 40%. Some studies,<sup>1,14,21,22</sup> but not all,<sup>1,11,23-25</sup> support a reduction in breast cancer risk. The varying results may be due to age differences in the study populations, differences in physical activity measures used, or duration of follow-up after recording recent or current activity.

Of interest in this study is the inverse association between long-term physical activity and ER- breast cancer, as tamoxifen and raloxifene have not affected ER- breast cancer incidence in chemoprevention trials.<sup>26,27</sup> The few previous studies<sup>9-12</sup> evaluating the effect of physical activity on invasive breast cancer risk by hormone receptor status suggest little or no difference in risk. Although we previously reported no difference in the impact of lifetime physical activity on joint ER and PR status for premenopausal and postmenopausal women,<sup>12</sup> close inspection of the results suggests a stronger protective association for ER-/PR- than for ER+/PR+ breast cancer. Exercise during adolescence and in the past 10 years was associated with a reduced risk of ER+/PR+ and ER-/PR- breast cancer in a Shanghai-based case-control study.<sup>9</sup> Similarly, we reported that the beneficial impact of exercise activity did not vary by ER status in a population-based case-control study<sup>10</sup> of white and black women in the United States. Thus, the present finding that physical activity reduces the risk of ER- tumors is consistent with the limited case-control study results, but the finding of no association for ER+ is not. The Women's Health Study<sup>11</sup> evaluated the effect of physical activity on hormone receptor-positive tumors and observed no significant associations, consistent with the results presented herein.

An association between long-term physical activity and breast cancer that is restricted to ER- tumors seems inconsistent with the hypothesis that physical activity acts through estrogen mediated by its receptor<sup>28-30</sup> and suggests that physical activity does not exert its biological effects wholly through hormonal mechanisms. However, these findings do not preclude a hormonal mechanism, as some evidence exists that when ER+ progenitor cells are exposed to estrogen, they produce paracrine signals, which cause the proliferation of nearby ER- cells.<sup>31</sup> Furthermore, the Breast and Prostate Cancer Cohort Con-

sortium showed that 2 common haplotypes of the 17 $\beta$ -hydroxysteroid dehydrogenase 1 gene (*HSD17B1*) are associated with risk of ER- but not ER+ breast cancer.<sup>32</sup> This gene encodes 17HSD1, which affects the conversion of estrone to estradiol, providing another potential link between estrogen and ER- tumors. The reduction in risk for ER- invasive breast cancer suggests that physical exercise may reduce tumor aggressiveness. Although this finding has enormous public health and therapeutic implications, it needs to be replicated in other studies, particularly in studies in which receptor status results collected through cancer registries can be verified in a single laboratory.

Few studies<sup>13,14,21</sup> have investigated the relationship between physical activity and in situ breast cancer. We previously reported a significant protective effect of lifetime physical activity on in situ breast cancer risk in a case-control study.<sup>13</sup> Physical activity at study entry was not associated with in situ breast cancer among 205 cases diagnosed in a cohort study of postmenopausal women.<sup>21</sup> The Women's Health Initiative Cohort Study<sup>14</sup> reported that women who engaged in strenuous physical activity at least 3 times per week at age 35 years had a modest, but not statistically significant, reduction in risk of in situ breast cancer; however, no specific data were provided in the publication. The present results support a protective effect of lifetime physical activity on the risk of in situ breast cancer. Most of these cancers are ductal carcinomas in situ, which are most often identified by mammography. The results for women with a screening mammogram within 2 years of baseline were consistent with those of the entire cohort. Thus, greater health consciousness of women is not a likely explanation for these findings. The risk reduction for in situ breast cancer suggests that physical activity acts at early stages in the development of breast cancer.

We did not identify ages when physical activity might have its greatest impact on breast cancer. We observed reductions in invasive and in situ breast cancer for activity at ages 25 to 34 years and 35 to 44 years that were similar to the long-term activity results. The modest, but not statistically significant, impact of activity during high school and at ages 18 to 24 years, coupled with the apparent greater impact of physical activity on invasive breast cancer among women younger than 55 years, may reflect greater misclassification of physical activity at younger ages, particularly among older women. In a recent case-control study,<sup>10</sup> which collected detailed age-specific data on physical activity using a calendar of life events, we also did not identify any particular ages when activity was most protective against breast cancer risk.

Several previous studies have looked at the effects of physical activity on breast cancer risk by subgroups of BMI<sup>14,21,23,24,33-35</sup> and family history,<sup>14,33,35-41</sup> but the results are inconsistent. Although we observed statistically significant results for younger women, women without a first-degree family history of breast cancer, leaner (BMI <25 or <30) women, and parous women, trends across the levels of these subgroups differed statistically significantly only for parity and invasive breast cancer.

The present results suggest that high levels of sustained strenuous but not moderate physical activity

reduce breast cancer risk. Although this may be simply a dose threshold effect, an alternative explanation is that women can recall their participation in intense activities more accurately.<sup>1,42</sup> Previous cohort studies<sup>1,14,35</sup> supporting an inverse association with recreational physical activity have varied in terms of intensity levels measured and levels that confer a reduction in risk.

Strengths of this study include its prospective design, cohort size, large number of incident invasive and in situ breast cancer cases, and ability to identify and confirm cancer diagnoses through California's high-quality statewide cancer registry. We collected detailed measures of physical activity in multiple age periods, allowing for the assessment of cumulative long-term physical activity and recent activity.

A potential limitation of this study is that we did not collect information on occupational or household physical activity. These additional sources of physical activity may be important contributors to total energy expenditure<sup>1,41</sup> and may affect the association between physical activity and breast cancer risk.<sup>1,37,41</sup> A Canadian case-control study<sup>37</sup> examined all 3 sources of physical activity and reported an inverse association with occupational and household activity but not with recreational activity. The California Teachers Study cohort consists of active and retired teachers and administrators, and although we did not measure occupational activity, it is likely that most women who are active in the California public school system would have similar occupational activity levels, with the possible exception of physical education teachers. However, the length of time that the active teachers had been employed in the school system varies substantially, and we do not have information on other occupations held. We collected information on strenuous and moderate levels of physical activity by self-report, providing examples of activities at each level. Although it is possible that the reported levels may overestimate or underestimate actual activity, information was collected before breast cancer diagnosis and should not differ by disease status overall or by receptor status of the tumor.

In summary, these results provide additional evidence supporting a protective role for long-term strenuous recreational physical activity on risk of invasive and in situ breast cancer, whereas the beneficial effects of moderate activity are less clear. For invasive breast cancer, strenuous and moderate activity affect risk of ER- tumors, but neither affect risk of ER+ tumors.

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