Lifetime Recreational Exercise Activity and Breast Cancer Risk Among Black Women and White Women

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Background: **Physical inactivity is a potentially modifiable breast cancer risk factor. Because few data on this relationship exist for black women, we examined the relationship between breast cancer risk and lifetime and time- or age-specific measures of recreational exercise activity among white women and among black women.** ***Methods:*** **The Women's Contraceptive and Reproductive Experiences Study was a multicenter population-based case–control study of black women and white women aged 35–64 years with newly diagnosed invasive breast cancer. We collected detailed histories of lifetime recreational exercise activity during in-person interviews with 4538 case patients with breast cancer (1605 black and 2933 white) and 4649 control subjects (1646 black and 3033 white). Control subjects were frequency-matched to case patients on age, race, and study site. We examined associations between exercise activity measures (metabolic equivalents of energy expenditure [MET]-hours per week per year) and breast cancer risk overall and among subgroups defined by race, other breast cancer risk factors, and tumor characteristics by use of unconditional logistic regression. All statistical tests were two-sided.** ***Results:*** **Among all women, decreased breast cancer risk was associated with increased levels of lifetime exercise activity (e.g., average MET-hours per week per year, P_{trend} = .002). An average annual lifetime exercise activity that was greater than the median level for active control subjects was associated with an approximately 20% lower risk of breast cancer, compared with that for inactivity (for 6.7–15.1 MET-hours/week/year, odds ratio [OR] = 0.82, 95% confidence interval [CI] = 0.71 to 0.93; for ≥15.2 MET-hours/week/year, OR = 0.80, 95% CI = 0.70 to 0.92). The inverse associations did not differ between black and white women (for MET-hours/week/year, P_{trend} = .003 and P_{trend} = .09, respectively; homogeneity of trends P = .16). No modification of risk was observed by disease stage, estrogen receptor status, or any breast cancer risk factor other than first-degree family history of breast cancer.** ***Conclusions:*** **This study supports an inverse association between physical activity and breast cancer among black women and among white women. [J Natl Cancer Inst 2005;97:1671–9]**

Physical activity has been proposed as a means for reducing women's risk of breast cancer *(1)* because of its potential impact on circulating hormones *(1–5)*, body mass *(6–9)*, and insulin sensitivity *(8)*. More than 30 studies have examined the association between recreational physical activity and breast cancer. Overall, study results support the hypothesis that regular physical activity is associated with reduced breast cancer risk *(10)*.

What remains unclear is the amount of lifetime activity necessary to reduce risk (if the association is causal), whether the benefits of activity vary by age, and whether the reduction in risk is observed in all population subgroups. For example, only one study has addressed the issue of physical activity in relation to breast cancer among black women, a case–control study of prevalent breast cancers nested within a cohort of black women *(11)*. Results of another study suggested that physical activity has less benefit for women with a family history of breast cancer *(12)*. To understand the association between physical activity and breast cancer risk better, we examined the relationship between lifetime and time- or age-specific measures of recreational exercise activity and breast cancer risk among white women and black women, and among women with and without a family history of breast cancer, in a large multicenter, population-based case–control study. We also evaluated whether the relationship was modified by any other breast cancer risk factors or by tumor characteristics.

Participants and Methods

Study Background

The Women's Contraceptive and Reproductive Experiences Study is a population-based case–control study that was designed

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to examine predictors of risk for invasive breast cancer among white women and black women. Five sites participated in this study: Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle. All study participants were white (including Hispanics) or black, English speaking, U.S. born, and aged 35–64 years, with no previous diagnosis of in situ or invasive breast cancer. A full description of the study methods, including extensive details on subject identification, recruitment, and participation rates, has been previously provided *(13)*.

Case patients were women diagnosed with histologically confirmed invasive breast cancer [International Classification of Diseases for Oncology codes C50.0–C50.9 *(14)*] between July 1, 1994, and April 30, 1998. In Atlanta, Detroit, Los Angeles, and Seattle, these patients were identified by the Surveillance, Epidemiology and End Results (SEER) cancer registries. In Philadelphia, patients were identified by field staff who contacted hospitals in the study area. Black women were oversampled to maximize their numbers in the study, and white women were randomly sampled to provide approximately equal numbers of women in each 5-year age category (35–39, 40–44, 45–49, 50–54, 55–59, and 60–64 years). Of the 5982 eligible case patients identified, we interviewed 4575 (76.5%), including 2953 white women (79.1% of eligible case patients) and 1622 black women (72.2% of eligible case patients). Of those eligible case patients who were not interviewed, 523 (8.7%) refused to participate; physicians refused permission to contact 235 (3.9%); we were unable to schedule an interview within the appropriate time frame (within 18 months of diagnosis or prior to study end date) or could not locate the patient for 395 (6.6%); 149 (2.5%) died before interview; and a variety of reasons accounted for the remaining 105 (1.8%) who were not interviewed. We extracted stage of breast cancer at diagnosis and estrogen receptor (ER) status from SEER registry records at the four SEER sites and from medical records in Philadelphia.

Random-digit dialing methods were used to identify control subjects from the geographic regions of corresponding case patients. During screening telephone calls, a census of potentially eligible women was created for each household contacted. Control subjects were randomly selected from the pool of women identified and were frequency-matched to case patients within strata of geographic site, race, and 5-year age group. Approximately 82% of residential households contacted were successfully screened. Of the 5956 eligible women (2212 black women and 3744 white women) who were selected as control subjects, 4682 (78.6%) were interviewed; 3021 (80.7%) were white and 1661 (75.1%) were black. Among eligible women we attempted to recruit, 774 (13.0%) refused to participate; we could not schedule an interview within the appropriate time frame (within 18 months of initial telephone contact with the household or prior to study end date) or were unable to locate 352 (5.9%); and we were unable to interview 148 (2.5%) for a variety of reasons.

Eligible subjects were first contacted by letter and then by telephone to schedule an in-person interview. During the telephone contact, standardized questions were asked by the interviewers to establish eligibility. All participants provided written informed consent before the in-person interview. The study was approved by the institutional review board at each institution involved in this collaborative study, in accord with assurances filed with and approved by the U.S. Department of Health and Human Services.

Information was collected during the interview up to a reference date that was defined for each case patient as the date of diagnosis and for each control subject as the date of contact with the household during the random-digit dialing screening process. Study subjects provided information on demographic and reproductive factors, including ages at menarche, menopause, and all pregnancies; pregnancy outcomes; lactation history; use of oral contraceptives and hormonal therapies; type of menopause if postmenopausal; family history of breast cancer; body size measures; lifestyle (history of exercise activity, smoking, and alcohol consumption); and frequency of mammographic screening in the 5 years before the reference date. Each participant was required to have a working residential telephone on her reference date and to be interviewed within 18 months of her reference date; 77% of interviewed case patients and 88% of interviewed control subjects were interviewed within 6 months of their reference dates.

We excluded nine case patients and four control subjects for whom information on exercise activity was missing and 28 case patients and 29 control subjects for whom information was missing for at least one of the following items: age at menarche, age at first term pregnancy (>26 weeks), total number of term pregnancies, total months of breast-feeding, or body mass index [weight in kilograms/(height in meters)^2] 5 years before the reference date. A total of 4538 case patients and 4649 control subjects were included in our analyses.

Measures of Exercise Activity

Recreational exercise activity was recorded after completion of a calendar of life events, on which we had recorded all pregnancy and contraception information. We documented all episodes of exercise activity in which a participant engaged throughout her lifetime up to her reference date and recorded details of activities in chronologic order starting with the first activity recalled by the respondent. For each activity episode, we recorded the type of activity, the age at which the woman started and stopped the activity, the number of months per year of participation in the activity, and the average duration in hours per week. Initially, women were instructed to report only those exercise activities in which they engaged at least 2 hours/week for at least 4 months. After completing interviews with 385 case patients and 488 control subjects, we changed this instruction so that women would include activities in which they engaged at least 1 hour/week for at least 4 months at any given age (4153 case patients and 4161 control subjects). We recorded all activities that women provided including any organized sports activities, such as school sports or teams, and individual activities, such as walking, jogging, running, hiking, bicycling, aerobics, swimming, and dancing. We also recorded details as to the extent of the activity (for example, recreational swimming, snorkeling, swimming laps, or training for competitive swimming).

We calculated the average number of hours of exercise activity per week for each year of age for each participant. We considered women to be inactive at any given age if they reported no activity for that age or if their average number of hours per week of activity for that age was less than 0.67 hour (i.e., equivalent to less than 2 hours/wk for 4 months). We then estimated the metabolic equivalents of energy expenditure (MET)-hours per week for each age by multiplying together the number of hours per

week a woman spent in a particular activity, the proportion of the year spent in that activity, and the estimated MET score for the activity based on the Compendium of Physical Activities *(15)*. As a measure of lifetime activity, we calculated average annual exercise activity from age 10 years to the woman's age on her reference date in hours per week and in MET-hours per week. We also calculated the average number of hours per week and the average number of MET-hours per week for the following times: ages 10–19 years, the first 10 years after menarche, ages 20–34 years, and the 10 years before a woman's reference date. For variables representing average hours per week and average MET-hours per week of exercise activity, we categorized women by approximate quartiles of the distribution of all control subjects classified as active.

Statistical Analyses

We used unconditional logistic regression modeling *(16)* to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) to examine the relationship between measures of exercise activity and breast cancer risk. Women who were classified as inactive at all ages were used as the referent group. For each analysis, we assessed risk associated with exercise activity in two models. In the first model, we adjusted for age (continuous), race (white or black), study site (Atlanta, Detroit, Los Angeles, Philadelphia, or Seattle), and type of questionnaire on exercise activity (original or modified). In the second model, we adjusted for these variables as well as for potential confounding factors that were selected a priori because of their fairly well-established relationship with breast cancer risk.

The potential confounding factors included in the multivariable models were family history of breast cancer in mother, sisters, or daughters (first-degree family history: yes, no, or unknown/adopted); age at menarche (continuous); body mass index at 5 years before the reference date (continuous); age at menopause (premenopausal, ages <35, 35–39, 40–44, 45–49, 50–54, or ≥55 years, or menopausal status not able to be determined or age unknown); number of term pregnancies (continuous); age at first term pregnancy (ages <20, 20–24, 25–29, 30–34, or ≥35 years or nulliparous); and total months of breast feeding (continuous). A woman was considered postmenopausal if, before her reference date, she had experienced a final menstrual period followed by a 12-month period with no menstrual period and no hormonal therapy (natural menopause), if she reported a bilateral oophorectomy (surgical menopause), or if her menstrual periods stopped because of radiation or chemotherapy at least 12 months before her reference date. We considered a woman to be premenopausal if she had any menstrual periods during the 12 months before her reference date and if she was not taking hormone replacement therapy. We were unable to determine menopausal status for women who had a hysterectomy and no bilateral oophorectomy when still having menstrual periods or within 12 months of their last menstrual period and women who began hormonal therapy while still menstruating or within 12 months of the last menstrual period.

Trend tests for each exercise activity variable were performed by fitting the median value of exercise activity within each of the categories as a continuous variable. When examining exercise activity trends during a specific time period, women who engaged in exercise activity only in other time periods were not included in the trend models so that the reference group was restricted to women considered to have no lifetime activity. To test whether the association between exercise activity and breast cancer risk was modified by other factors, we used a likelihood ratio test comparing two multivariable logistic regression models. We examined effect modification by age (<50 years versus ≥50 years), race (black versus white), first-degree family history of breast cancer (yes versus no, excluding those with unknown status), parity (nulliparous versus parous women), body mass index (<25 kg/m^2 versus ≥25 kg/m^2), menopausal status (premenopausal versus postmenopausal, excluding those with unknown menopausal status), ever used oral contraceptives (no versus yes), and ever used any type of hormone replacement therapy among postmenopausal women (no versus yes). The base model, which included one variable for exercise activity trend, was compared with a model with two variables for exercise activity trend, one for each of the two categories of the potential effect modifier (likelihood ratio test for heterogeneity of trends with 1 *df*) *(17)*. We also examined risk by stage of disease (local versus nonlocal) and ER status (ER-negative versus ER-positive tumors) by comparing each subgroup with all control subjects and then conducting an analysis restricted to case patients. For subgroup analysis, we present only the results from fully adjusted models. All *P* values reported are from tests of two-sided alternative hypotheses. We did not adjust for multiple comparisons.

Results

The average age at diagnosis for case patients was 49.7 years (standard deviation [SD] = 8.4 years), and the average age on the reference date for control subjects was 49.5 years (SD = 8.3 years). Thirty-five percent of both case patients and control subjects were black. The distributions of covariates considered in the multivariable logistic regression models are shown in Table 1.

In this study, 1132 (24.9%) of a total of 4538 case patients and 1083 (23.3%) of 4649 control subjects reported no exercise activity between age 10 years and the reference date (Table 2). More than 400 types of exercise activities or combinations of activities were reported by study participants. The most frequently reported activities were walking for exercise (54% of both case patients and control subjects), aerobics (27% of each group), and bicycling (21% of case patients and 22% of control subjects). Other activities reported by more than 10% of the participants were recreational swimming, softball and/or baseball, jogging and/or running, gymnasium workouts, tennis, and basketball.

The risk of invasive breast cancer was approximately 20% lower among women in the highest two of five categories for lifetime exercise activity (expressed as annual hours per week or annual MET-hours per week), compared with that of inactive women (e.g., OR of breast cancer for second highest category [6.7–15.1 MET-hours/week/year] = 0.82, 95% CI = 0.71 to 0.93; and OR of breast cancer for the highest category [≥15.2 MET-hours/week/year] = 0.80, 95% CI = 0.70 to 0.92) (Table 2). We observed an inverse trend in breast cancer risk across all categories of lifetime exercise activity with increasing levels of activity, measured either by average annual hours per week (P_{trend} = .003) or by average annual MET-hours per week (P_{trend} = .002). The associations for specific periods of life (10 years after menarche, ages 10–19 years, ages 20–34 years, and the

Table 1. Distribution of covariates by case (n = 4538) and control (n = 4649) status

Covariate	No. case patients (%)	No. control subjects (%)
Reference age		
35–39 y	681 (15.0)	658 (14.2)
40–44 y	753 (16.6)	827 (17.8)
45–49 y	777 (17.1)	855 (18.4)
50–54 y	838 (18.5)	818 (17.6)
55–59 y	765 (16.9)	794 (17.1)
60–64 y	724 (15.9)	697 (15.0)
Race		
White	2933 (64.6)	3003 (64.6)
Black	1605 (35.4)	1646 (35.4)
Study site		
Atlanta	875 (19.3)	887 (19.1)
Detroit	672 (14.8)	772 (16.6)
Los Angeles	1237 (27.2)	1247 (26.8)
Philadelphia	702 (15.5)	732 (15.8)
Seattle	1052 (23.2)	1011 (21.7)
Physical activity questionnaire		
Original	385 (8.5)	488 (10.5)
Modified	4153 (91.5)	4161 (89.5)
First-degree family history of breast cancer*		
No	3586 (79.0)	4021 (86.5)
Yes	775 (17.1)	450 (9.7)
Adopted/unknown	177 (3.9)	178 (3.8)
Age at menarche		
≤11 y	1184 (26.1)	1253 (26.9)
12 y	1334 (29.4)	1245 (26.8)
13 y	1188 (26.2)	1209 (26.0)
≥14 y	832 (18.3)	942 (20.3)
Age at menopause		
Premenopausal	2102 (46.3)	2045 (44.0)
<35 y	56 (1.2)	127 (2.7)
35–39 y	92 (2.0)	159 (3.4)
40–44 y	211 (4.7)	268 (5.8)
45–49 y	436 (9.6)	441 (9.5)
50–54 y	409 (9.0)	357 (7.7)
≥55 y	86 (1.9)	66 (1.4)
Menopausal status not determined†	1146 (25.3)	1186 (25.5)
Age at first term pregnancy (>26 wk)		
<20 y	1040 (22.9)	1184 (25.5)
20–24 y	1356 (29.9)	1457 (31.3)
25–29 y	771 (17.0)	714 (15.4)
30–34 y	345 (7.6)	347 (7.5)
≥35 y or nulliparous	1026 (22.6)	947 (20.4)
No. of term pregnancies (>26 wk)		
0	882 (19.4)	801 (17.2)
1	767 (16.9)	716 (15.4)
2	1360 (30.0)	1353 (29.1)
3	839 (18.5)	897 (19.3)
4	379 (8.4)	442 (9.5)
≥5	311 (6.9)	440 (9.5)
No. of months of breast-feeding		
Never breast-fed	2594 (57.2)	2395 (51.5)
≤6 mo	1076 (23.7)	1197 (25.7)
7–15 mo	449 (9.9)	521 (11.2)
≥16 mo	419 (9.2)	536 (11.5)
Body mass index at 5 years before reference date‡		
<22.5 kg/m^2	1504 (33.1)	1479 (31.8)
22.5–24.9 kg/m^2	1014 (22.3)	986 (21.2)
25–27.4 kg/m^2	766 (16.9)	786 (16.9)
≥27.5 kg/m^2	1254 (27.6)	1398 (30.1)

*Mother, sister, or daughter.

†This category includes women who had a hysterectomy and no bilateral oophorectomy when still having menstrual periods or within 12 months of their last menstrual period, women who began taking hormone therapy while still menstruating or within 12 months of their last menstrual period, or women with unknown age at menopause.

‡Reference date is case patient's date of diagnosis or the date of contact with the household during the random digit dialing screening process for control subjects.

10 years before the reference date) were similar to the associations for lifetime exercise activity (data not shown). For example, breast cancer risk was inversely associated with average annual MET-hours of exercise activity in the 10 years before the reference date (P_{trend} = .013) and in the 10 years after menarche (P_{trend} = .028).

Black women were more likely than white women to be classified as inactive (Table 3). Among 4538 case patients, 542 (33.8%) of the 1605 black women but only 590 (20.1%) of the 2933 white women were inactive. Among the 4649 control subjects, 535 (32.5%) of the 1646 black control subjects and 548 (18.2%) of the 3003 white control subjects were inactive. We observed no statistically significant inverse trends in breast cancer risk with an increasing level of lifetime exercise activity for white women (for average annual hours per week, P_{trend} = .16; and for average annual MET-hours per week, P_{trend} = .09), although the risk estimates for each exercise category were all below 1.0 and the confidence intervals for three of the four activity categories excluded 1.0 (Table 3). For black women, we observed a statistically significant inverse association with increasing level of lifetime exercise activity (for average annual hours per week, P_{trend} = .002; and for average annual MET-hours per week, P_{trend} = .003). Nevertheless, we observed no effect modification by race (for average annual hours per week, heterogeneity of trends P = .08; and for average annual MET-hours per week, P = .15).

We found no evidence that age (<50 years versus ≥50 years), parity (nulliparous versus parous), body mass index (<25 kg/m^2 versus ≥25 kg/m^2), menopausal status (premenopausal versus postmenopausal), use of hormone replacement therapy by postmenopausal women (no versus yes), or use of oral contraceptives (no versus yes) modified the association between lifetime exercise activity and breast cancer risk (data not shown). However, the patterns of risk differed for women with or without a first-degree family history of breast cancer (for average annual hours per week, heterogeneity of trends P = .014; and for average annual MET-hours per week, P = .007) (Table 4). We observed no association of physical activity with breast cancer risk for women with a positive first-degree family history of breast cancer (for average annual hours per week, P_{trend} = .23; for average annual MET hours per week, P_{trend} = .18). However, breast cancer risk progressively decreased with increasing level of exercise activity among women with no family history of breast cancer (for average annual hours per week, P_{trend}<.001; and for average annual MET hours per week, P_{trend}<.001) (Table 4).

Information on tumor receptor status was available for 1301 (81.1%) of 1605 black case patients and 2636 (89.9%) of 2933 white case patients for a total of 3937 (86.8%) of 4538 case patients overall. The relative odds of ER-positive and ER-negative breast cancer declined with increasing lifetime MET-hours of exercise activity (Table 5), but only the result for ER-positive tumors was statistically significant (P_{trend} = .009 versus P_{trend} = .111). Nevertheless, when we compared ER-positive case patients with ER-negative case patients, we found no effect modification by ER status (P_{trend} = .47). In addition, we found no difference in risk patterns for women with localized versus more advanced disease (data not shown).

We, finally, considered whether body mass index might be an intermediate variable on the pathway between exercise activity and breast cancer risk by repeating the analyses without body mass index in the multivariable logistic regression model. Results

Table 2. Relative odds of invasive breast cancer associated with lifetime exercise activity*

Lifetime average exercise activity	No. case patients (n = 4538)	No. control subjects (n = 4649)	OR† (95% CI)	OR‡ (95% CI)
Annual h/wk				
Inactive	1132	1083	1.00 (referent)	1.00 (referent)
≤0.4 h/wk	871	878	0.94 (0.83 to 1.07)	0.92 (0.81 to 1.05)
0.5–1.2 h/wk	862	873	0.93 (0.81 to 1.05)	0.88 (0.77 to 1.01)
1.3–2.9 h/wk	845	907	0.87 (0.77 to 0.99)	0.82 (0.72 to 0.93)
≥3.0 h/wk	828	908	0.86 (0.75 to 0.97)	0.81 (0.71 to 0.92)
P_{trend}			.024	.003
Annual MET-h/wk				
Inactive	1132	1083	1.00 (referent)	1.00 (referent)
≤2.2 MET-h/wk	874	872	0.95 (0.84 to 1.08)	0.93 (0.82 to 1.06)
2.3-6.6 MET-h/wk	895	915	0.92 (0.81 to 1.04)	0.87 (0.77 to 0.99)
6.7-15.1 MET-h/wk	822	881	0.87 (0.77 to 0.99)	0.82 (0.71 to 0.93)
≥15.2 MET-h/wk	815	898	0.85 (0.75 to 0.97)	0.80 (0.70 to 0.92)
P_{trend}			0.018	0.002

*Lifetime is defined as being from age 10 years to reference date; reference date is case patient's date of diagnosis or the date of contact with the household during the random digit dialing screening process for control subjects. OR = odds ratio; CI = confidence interval; MET = metabolic equivalent of energy expenditure. P_{trend} values are two-sided and were derived from the Wald test.

†Adjusted for age, race, study site, and exercise activity questionnaire type.

‡Adjusted for age; race; study site; exercise activity questionnaire type; history of breast cancer in a mother, sister or daughter; age at menarche; menopausal status and age at menopause; age at first term pregnancy (>26 weeks); total number of term pregnancies (>26 weeks); body mass index at 5 years before reference date; and number of months of breast-feeding.

for all exercise activity variables were similar to those presented in Tables 2–5. We also assessed whether the number of mammograms women had in the 5 years before the reference date affected the estimates of risk by adding this variable to the multivariable models. This information was missing for 29 case patients and 20 control subjects. Results of these models provided the same trends in risk as the multivariable models presented in Tables 2–5.

Discussion

In this case–control study, we observed a modest, but statistically significant, decreasing breast cancer risk associated with increasing physical activity levels averaged over a woman's lifetime (from age 10 years to the reference age). An annual average of at least 1.3 hours of exercise activity per week (or 6.7 MET-hours of exercise activity per week) from age 10 years onward was associated with nearly a 20% reduction in breast cancer risk. These findings for lifetime activity are consistent with those of most previous studies that have examined lifetime recreational physical activity in relation to breast cancer risk *(10)*. Notably, in this study, higher levels of lifetime exercise activity were associated with lower breast cancer risk among black women. To our knowledge, only one other study *(11)* has provided results on physical activity and breast cancer among black women. That

Table 3. Lifetime exercise activity and relative odds of invasive breast cancer stratified by race*

Lifetime average exercise activity	White		Black	
	No. case patients (n = 2933)/ No. control subjects (n = 3003)	OR† (95% CI)	No. case patients (n = 1605)/ No. control subjects (n = 1646)	OR† (95% CI)
Annual h/week				
Inactive	590/548	1.0 (referent)	542/535	1.0 (referent)
≤0.4 h/wk	531/587	0.82 (0.70 to 0.97)	340/291	1.11 (0.91 to 1.36)
0.5–1.2 h/wk	606/595	0.90 (0.76 to 1.06)	256/278	0.84 (0.68 to 1.04)
1.3–2.9 h/wk	619/656	0.81 (0.69 to 0.96)	226/251	0.81 (0.65 to 1.01)
≥3.0 h/wk	587/617	0.83 (0.70 to 0.98)	241/291	0.75 (0.61 to 0.93)
P_{trend}		.16		.002
		P for heterogeneity of trends = .08		
Annual MET-h/wk				
Inactive	590/548	1.0 (referent)	542/535	1.0 (referent)
≤2.2 MET-h/wk	525/571	0.84 (0.71 to 0.99)	349/301	1.11 (0.91 to 1.35)
2.3–6.6 MET-h/wk	632/627	0.89 (0.75 to 1.04)	263/288	0.83 (0.67 to 1.03)
6.7–15.1 MET-h/wk	608/639	0.82 (0.69 to 0.97)	214/242	0.79 (0.63 to 0.99)
≥15.2 MET-h/wk	578/618	0.81 (0.69 to 0.96)	237/280	0.77 (0.62 to 0.95)
P_{trend}		.09		.003
		P for heterogeneity of trends = .15		

*Lifetime was defined as being from age 10 years to reference date; reference date is case patient's date of diagnosis or the date of contact with the household during the random digit dialing screening process for control subjects. OR = odds ratio; CI = confidence interval; MET = metabolic equivalent of energy expenditure. P_{trend} values were derived from the Wald test. P values for the tests for heterogeneity of trends were derived from the likelihood ratio test. All P values are two-sided.

†Adjusted for age; study site; race; exercise activity questionnaire type; history of breast cancer in a mother, sister, or daughter; age at menarche; menopausal status and age at menopause; age at first term pregnancy (>26 wk); total number of term pregnancies (>26 wk); body mass index at 5 years before reference date; and number of months of breast-feeding.

Table 4. Lifetime exercise activity and relative odds of invasive breast cancer stratified by first-degree family history of breast cancer*

Lifetime average exercise activity	No family history of breast cancer		Family history of breast cancer	
	No. case patients (n = 3586)/ No. control subjects (n = 4021)	OR† (95% CI)	No. case patients (n = 775)/ No. control subjects (n = 450)	OR† (95% CI)
Annual h/wk				
Inactive	874/914	1.0 (referent)	192/111	1.0 (referent)
≤0.4 h/wk	694/758	0.93 (0.81 to 1.07)	144/88	0.91 (0.63 to 1.30)
0.5–1.2 h/wk	702/749	0.91 (0.79 to 1.05)	139/89	0.84 (0.59 to 1.21)
1.3–2.9 h/wk	666/789	0.81 (0.70 to 0.94)	153/96	0.82 (0.58 to 1.17)
≥3.0 h/wk	650/811	0.77 (0.66 to 0.89)	147/66	1.18 (0.81 to 1.73)
P_{trend}		<.001		.23
		P for heterogeneity of trends = .014		
Annual MET-h/wk				
Inactive	874/914	1.0 (referent)	192/111	1.0 (referent)
≤2.2 MET-h/wk	697/751	0.94 (0.82 to 1.08)	146/84	0.98 (0.68 to 1.40)
2.3–6.6 MET-h/wk	727/790	0.90 (0.78 to 1.03)	142/96	0.78 (0.55 to 1.12)
6.7–15.1 MET-h/wk	650/759	0.82 (0.71 to 0.95)	149/96	0.79 (0.56 to 1.13)
≥15.2 MET-h/wk	638/807	0.75 (0.65 to 0.87)	146/63	1.25 (0.85 to 1.83)
P_{trend}		<.001		.18
		P for heterogeneity of trends = .007		

*Lifetime is defined as being from age 10 years to reference date; reference date is case patient's date of diagnosis or the date of contact with the household during the random digit dialing screening process for control subjects. First-degree family history of breast cancer is defined as having a mother, sister, or daughter who was diagnosed with breast cancer. Results were based on 4361 (96.1%) of 4538 case patients and 4471 (96.2%) of 4649 control subjects who were able to report their family histories of breast cancer. OR = odds ratio; CI = confidence interval; MET = metabolic equivalent of energy expenditure. P_{trend} values were derived from the Wald test. P values for the tests for heterogeneity of trends were derived from the likelihood ratio test. All P values are two-sided.

†Adjusted for age; race; study site; exercise activity questionnaire type; history of breast cancer in a mother, sister, or daughter; age at menarche; menopausal status and age at menopause; age at first term pregnancy (>26 wk); total number of term pregnancies (>26 wk); body mass index at 5 years before reference date; and number of months of breast-feeding.

study was based on prevalent cases of breast cancer among women at the time they joined a newly forming cohort of black women. In that study, high levels of strenuous physical activity during women's early adult years were associated with a reduced relative odds of prevalent breast cancer. Our results for black women add to existing data on other groups of women defined by race or ethnicity *(18–22)* and geography *(23–26)*. Risk estimates for white women with low levels of lifetime exercise activity were similar to estimates for those with higher levels of activity (the highest two categories of activity). Nevertheless, we found no effect modification by race.

All specific age and time periods of exercise activity examined were associated with reduced risks similar to that associated with average lifetime activity, so we were unable to identify an age or time of life when exercise activity had the greatest association with breast cancer risk. One reason we could not identify a time period when it would be most important to be physically active is because our lifetime activity measures are highly correlated with each of the age and time period measures and with each other. For example, Pearson correlation coefficients for our lifetime measures and our age- or time-specific measures ranged from .76 to .92 overall and for case patients and control subjects separately; similarly, the correlation coefficient between activity from ages 10 to 19 years and from ages 20 to 34 years was .60. The high correlations we observed confirm results reported by Alfano et al. *(27)*, who showed that women who are physically

Table 5. Lifetime exercise activity and relative odds of invasive breast cancer among women stratified by estrogen receptor (ER) status of tumor*

Lifetime average exercise activity	ER positive		ER negative		OR for ER-negative vs. ER-positive tumors (95% CI)‡
	No. case subjects (n = 2636)/ No. control subjects (n = 4649)	OR† (95% CI)	No. case subjects (n = 1301)/ No. control subjects (n = 4649)	OR† (95% CI)	
Annual MET-h/wk					
Inactive	624/1083	1.0 (referent)	327/1083	1.0 (referent)	1.0 (referent)
≤2.2 MET-h/wk	508/872	0.92 (0.79 to 1.07)	254/872	0.99 (0.82 to 1.20)	1.04 (0.84 to 1.29)
2.3–6.6 MET-h/wk	538/915	0.86 (0.74 to 1.00)	249/915	0.90 (0.74 to 1.09)	1.02 (0.83 to 1.27)
6.7–15.1 MET-h/wk	486/881	0.78 (0.67 to 0.91)	225/881	0.84 (0.69 to 1.03)	1.00 (0.80 to 1.25)
≥15.2 MET-h/wk	480/898	0.79 (0.68 to 0.93)	246/898	0.86 (0.70 to 1.05)	1.10 (0.88 to 1.37)
P_{trend}		.009		.11	.47

*Lifetime is defined as being from age 10 years to reference date; reference date is case patient's date of diagnosis or the date of contact with the household during the random digit dialing screening process for control subjects. Information on ER status was available for 3937 (86.8%) of 4538 case patients. OR = odds ratio; CI = confidence interval; MET = metabolic equivalent of energy expenditure. All statistical tests were two-sided. P_{trend} values were derived from the Wald test.

†Adjusted for age; race; study site; exercise activity questionnaire type; history of breast cancer in a mother, sister or daughter; age at menarche; menopausal status and age at menopause; age at first term pregnancy (>26 wk); total number of term pregnancies (>26 wk); body mass index at 5 years before reference date; and number of months of breast-feeding.

‡Analysis restricted to case patients; OR and 95% CI represent the odds of ER-negative breast cancer relative to the odds of ER-positive breast cancer according to level of exercise activity and provide information on whether any exercise activity effects are modified by the ER status of the tumor.

active during childhood and adolescence are more likely to be physically active as adults. Our results were remarkably similar for both metrics of activity—hours per week and MET-hours per week—and are also similar to those of Bernstein et al. *(28)*, who reported results for hours per week only, but noted that results for MET-hours per week were comparable.

We evaluated whether body mass index modified the association between exercise activity and breast cancer risk and found no evidence of any interaction, overall or by menopausal status. Several previous studies suggested modification of the association between physical activity and breast cancer by body mass index, although the body mass index subgroups for which the associations were strongest are not consistent across studies *(12,23,25,29–31)*.

Various biologic mechanisms have been proposed through which physical activity could, in theory, reduce the risk of breast cancer. Studies among athletes show that high levels of moderate and vigorous physical activity during the reproductive years affect markers of exposure to ovarian hormones, resulting in delayed menarche, increased likelihood of secondary amenorrhea, irregular or anovulatory menstrual cycles, and shortened luteal phases of the menstrual cycle *(2,28,32–35)*. Thus, physical activity is associated with lower concentrations of estradiol, progesterone, and follicle-stimulating hormone circulating in the blood, particularly during adolescence. Additional studies *(4,5)* suggest that ovarian function may be altered in recreational athletes who engage in less strenuous activity, through lower mean concentrations of hormones or longer menstrual cycles, although data are not as conclusive as those for athletes with higher levels of physical activity. Women who are physically active during the postmenopausal years have lower concentrations of serum estrone *(3,6)*, estradiol *(3,36)*, and androgens (androstenedione and testosterone), which are precursors to estrogens *(3,6)*, than inactive women. An association between physical activity and higher concentrations of sex hormone-binding globulin has also been observed *(8)*.

In addition, regular physical activity has been associated with higher insulin sensitivity and lower concentrations of serum insulin *(8,37)*. Higher concentrations of insulin have been associated with lower concentrations of sex hormone–binding globulin and, consequently, higher concentrations of bioavailable or free estradiol, which may increase breast cancer risk *(38)*. High levels of physical activity have been most consistently associated with lower weight, lower body mass index, and weight loss *(6–9,39)*. Maintenance of normal body weight is one of the few known ways to modify risk for breast cancer, and a lack of energy balance that results in excess adipose tissue is associated with many other potential mechanisms and risk factors for breast cancer such as insulin resistance *(40,41)* and higher concentrations of insulin-like growth factors *(41)*, total estradiol (via increased aromatase activity) *(42)*, and free estradiol (resulting from lower concentrations of sex hormone–binding globulin) *(8,42)*. Thus, the associations between physical activity and breast cancer risk may be due to the direct suppression of hormone concentrations or may be more indirect.

Family history of breast cancer may modify the association between exercise activity and breast cancer risk, because we observed no reduction in risk among women reporting a first-degree family history of breast cancer. However, it should be noted that only among women in the highest exercise activity categories (either ≥3 hours/wk/y or ≥15.2 MET-hours/week/year) was a difference in breast cancer risk by family history observed. For other categories of exercise activity, the risk for women with a family history was similar to that for women without such a history. Several other studies have examined how a family history of breast cancer modifies the association between exercise activity and breast cancer *(12,43–49)*. One study reported that family history modified the association between physical activity and breast cancer among postmenopausal women, with statistically significant trends in risk observed only among women with no family history of breast cancer *(12)*. The majority of women in this previous study were white. Hormonal differences by family history offer one possible explanation for the variation in risk by family history. Serum concentrations of estrone and estradiol have been shown to be higher in premenopausal women with a family history of breast cancer than in age-matched control subjects *(50)*. Therefore, it is biologically plausible that the impact of breast cancer risk factors mediated through hormonal pathways, such as physical activity, may differ by family history.

We evaluated whether the association between physical activity and breast cancer risk differed by ER status. Our results for ER-positive tumors did not differ from those for ER-negative tumors. Enger et al. *(51)* reported results on tumor receptor status from two case–control studies of breast cancer. In these studies, the risk for ER-positive/progesterone (PR)-positive, ER-positive/PR-negative, and ER-negative/PR-negative breast cancers decreased with increasing levels of physical activity.

Our study has several strengths, as well as several potential limitations. Among the strengths are the study's size, population-based sampling, geographic diversity, and inclusion of both black and white women. The detailed data that we obtained on exercise activity, by use of the calendar of life events to facilitate recall, permitted assessment of lifetime exercise activity, as well as activity during various age and time periods. This interview approach, known as cognitive interviewing, has proved to be a reliable method for collecting lifetime histories of exercise activity *(52)*. Further, this systematic method of collecting information on lifetime exercise should reduce the likelihood of biased reporting. Any misclassification is likely to be nondifferential, so that the associations we have found may be underestimates of the real associations.

A potential limitation for any case–control study is the possibility that selection bias or recall bias may have influenced the results. In regard to selection bias, we note that our response rates were relatively high and the findings for exercise activity were consistent across study sites. For example, the test for heterogeneity of trends in breast cancer risk associated with hours per week of exercise activity across the five study sites yielded a P value of .20. Recall bias was minimized by assessing exercise activity in conjunction with the completion of a calendar of life events to facilitate recall and by recording activities at every age throughout life. Nevertheless, recall bias cannot be ruled out in our study. A further limitation of our study is the lack of information on occupational and household activity. A study of women in Alberta, Canada, found no impact of recreational activity on breast cancer risk, but a statistically significant inverse association with occupational and household activity *(49)*.

In summary, this study further substantiates the association between physical activity and breast cancer risk. Our data suggest that regular exercise activity throughout a woman's life can decrease breast cancer risk and that the association of physical activity and breast cancer risk is not materially modified by race.

This study provides evidence of a reduction in risk among black women living in five geographic areas of the United States. The inverse association between physical activity and breast cancer risk may be more pronounced in women with no family history of breast cancer. We were not able to identify critical time periods in a woman's life when exercise is most beneficial, and we could not determine which activities or intensity of activities confer the greatest risk reduction.

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