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Research Article

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Adult Physical Activity and Breast Cancer Risk in Women with a Family History of Breast Cancer

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Abstract

Background: Recreational physical activity has been consistently associated with reduced breast cancer risk. Less is known about how family history of breast cancer affects the association and whether it varies by menopausal status.

Methods: The Sister Study is a cohort of 50,884 women who had a sister with breast cancer but no prior breast cancer themselves at enrollment. Women reported all recreational sport/exercise activities they participated in over the past 12 months. Hours/week and MET-hours/week of physical activity were considered in association with breast cancer risk. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated with Cox regression. Extent of family history, examined as a modifier, was characterized by a Bayesian score incorporating characteristics of the family structure.

Results: During follow-up (average 8.4 years), 3,023 cases were diagnosed. Higher hours/week ($HR_{\geq 7vs<1} = 0.77$; 95% CI, 0.66–0.90) and MET-hours/week ($HR_{quartile4vs1} = 0.75$; 95% CI, 0.67–0.85) of physical activity were associated with reduced postmenopausal breast cancer risk. Hours/week and MET-hours/week were associated with suggestively increased premenopausal breast cancer risk (MET-hours/week $HR_{quartile4vs1} = 1.25$; 95% CI, 0.98–1.60). Associations did not vary with extent of family history. However, the increased risk in premenopausal women may be limited to those with stronger family history.

Conclusions: In women with a family history of breast cancer, physical activity was associated with reduced postmenopausal, but not premenopausal, breast cancer risk and was not modified by extent of family history.

Impact: This was the first study to examine the association between physical activity and breast cancer risk in a large population with a family history of breast cancer.

Introduction

Adulthood physical activity has been consistently associated with reduced breast cancer risk (1, 2). In a meta-analysis of 27 cohort studies, the highest versus lowest level of recreational physical activity was associated with a relative risk (RR) of 0.87 [95% confidence interval (CI), 0.83–0.91] for breast cancer (1). Although the 2018 Physical Activity Guidelines for Americans scientific report similarly concluded that there is substantial evidence that higher amounts of physical activity reduce overall breast cancer risk, it also stated there is only limited evidence on the relationship in women at increased risk of breast cancer (3), such as those with a family history.

Women who have a family history of breast cancer in a first-degree relative are at twice the risk of breast cancer compared with women who do not (4, 5). Risk increases with the number of affected first-degree female relatives (6) and for women whose relatives were diagnosed at a younger age (5), indicating that extent of breast cancer family history also puts women at a differential risk. Women with a family history of breast cancer may have a heightened concern about their own risk (7) and they may be particularly interested in modifying their lifestyle to decrease their risk of breast cancer (8). Thus, it is important to determine whether physical activity, which has an established inverse association with breast cancer, is also associated with a reduced risk in women with a family history of breast cancer.

Results from studies examining whether the inverse association between physical activity and breast cancer risk is modified by a family history of breast cancer have been mixed (9–23). Previous studies have been limited by a small sample size in the family history group, making it difficult to draw conclusions about the association among those women. Further, all studies of physical activity to date examined first-degree family history as a dichotomous variable (yes/no), rather than incorporating details on extent of the family history.

An important consideration is whether associations among women with a family history of breast cancer differ for pre- versus postmenopausal breast cancer. Breast cancer risk is higher in women with a first-degree relative diagnosed before age 50 (5, 6), and a few studies have found that family history may be more strongly associated with premenopausal risk or diagnosis

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less than 50 years compared with postmenopausal risk or diagnosis after age 50 years (24, 25). A recent meta-analysis of 43 studies with premenopausal estimates and 58 studies with postmenopausal estimates reported that the highest versus lowest categories of recreational physical activity demonstrated a similar reduction in risk for premenopausal (RR = 0.80; 95% CI, 0.74–0.87) and postmenopausal (RR = 0.79; 95% CI, 0.76–0.84) breast cancer (26). Although this meta-analysis also looked at the associations by menopausal status in subgroups of those with and without a family history of breast cancer, only one study contained information on family history in premenopausal women. No studies have looked at the association between physical activity and both pre- and postmenopausal breast cancer in a population of women with a family history of breast cancer.

Given the unanswered questions in the literature, this study had three objectives: to examine (i) the association between physical activity and breast cancer in a large population of women who all have a family history of breast cancer; (ii) whether extent of the family history modifies the association; and (iii) whether the associations in the first two objectives vary by menopausal status.

Materials and Methods

Study population

The Sister Study is a prospective observational cohort study of 50,884 women, ages 35 to 74, focused on environmental and lifestyle risk factors for breast cancer (27). Recruitment occurred throughout the United States and Puerto Rico during 2003 to 2009. Women were eligible if they had a sister who had been diagnosed with breast cancer, but had no previous breast cancer diagnosis themselves at baseline.

At baseline, all women completed a comprehensive computer-assisted telephone interview (CATI), which assessed information on reproductive, demographic, and lifestyle factors; medical history; residential history; and environmental exposures. During follow-up, women are asked to complete an annual health update and detailed follow-up questionnaires every 2 to 3 years. Response rates have remained above 92% throughout follow-up (27).

All participants provided written informed consent. The study was approved by the National Institute of Environmental Health Sciences (NIEHS) and Copernicus Group institutional review boards. The present research utilized data-release 6.0, which includes follow-up through September 2016.

Physical activity exposure assessment

Recreational physical activity was assessed during the baseline interview. Women were asked to report all sport/exercise activities they had participated in at least once/week for at least 1 month during the past 12 months, how many months they did each activity, the number of days per week during those months they did the activities, and the amount of time per day. This was used to calculate the total average hours/week of recreational physical activity for the past 12 months.

MET (metabolic equivalent)-hours are an additional metric used to measure physical activity that incorporate the intensity of the activity in addition to the duration. Each physical activity is given a value that represents the multiple of the metabolic rate for that activity over the resting metabolic rate (28). For example, a one-MET activity represents the resting metabolic rate when sitting quietly, whereas a three-MET activity requires three times the energy expenditure as the resting metabolic rate. The compendium of MET values for various activities is listed in Ainsworth (2000; ref. 28).

We considered both hours/week and MET-hours/week in this study because each provides unique information and have different strengths and limitations. Hours/week are often used for public health messaging and recommendations because it is interpretable to the general public. Additionally, hours/week were calculated from the frequency and duration information that participants provided directly. Although METs additionally incorporate important information on intensity, a limitation is that researchers assign MET values with the compendium based on the description of the activity that the participants provide, rather than being directly measured.

Family history risk score

All women in the cohort, based on enrollment criteria, have at least one female relative with breast cancer, although for 4.2% of women this is only a half-sister (27). Excluding the women who had only a half-sister with breast cancer did not change the results, so all women were included. This study examines whether extent of family history is an effect-measure modifier of the physical activity–breast cancer associations. A novel breast cancer family history risk score was developed with the goal of improving over other classification metrics (e.g., "yes"/"no" or 0/1/1+ first-degree female relatives) that do not incorporate important characteristics such as family size and age at relatives' diagnosis. This more detailed family history information is important because, for example, a woman with many sisters whose affected sisters were diagnosed at older ages should be considered at lower risk than a woman with fewer sisters but those affected diagnosed at younger ages. Other earlier measures of family history risk were created that also accounted for family size and structure (29, 30), but the family history risk score used in this study is calculated under a Bayesian framework, was originally derived using the Sister Study population, and the value has a direct interpretation as the family-specific lifetime breast cancer risk (Y. Jiang, C.R. Weinberg, D.P. Sandler, S. Zhao; manuscript in preparation). We assume the lifetime risk of breast cancer, denoted p, for a specific family has a Beta distribution. The corresponding hazard function for age t is calculated as $\lambda_p(t) = f(p)\lambda_0(t)$, where the population hazard function (estimated from SEER registries) is represented by $\lambda_0(t)$, and the family-based variability arises through the multiplicative factor, $f(p)$. The contribution of each first-degree female relative is through the likelihood of her breast cancer experience weighted by the proportion of the hazard experienced up to her current diagnosis or death age. Through this Bayesian approach, important aspects of family history are incorporated, including family size, number of breast cancer cases, and diagnosis age or current/death age of first-degree female relatives. A calculated posterior mean of p assigns each woman a continuous Bayesian family history risk score between 0 and 1, which represents the lifetime risk for female members of that family. In the Sister Study population, the range is 0.082 to 0.698 with a median of 0.282.

Incident breast cancer

Women who report an incident breast cancer are subsequently asked for additional diagnosis information and permission to obtain medical records. Agreement between self-reported breast cancers and the medical records has been very high [positive

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predictive value (PPV) = 99.3%; ref. 31]. Therefore, self-report was used when medical records were not available (20% of participants). The present study excluded 163 women who were diagnosed with breast cancer before their enrollment was complete.

Statistical analysis

Hazard ratios (HR) and 95% CIs for breast cancer risk were determined using multivariable Cox proportional hazards regression with age as the time scale and person-time accrued from baseline until date of breast cancer diagnosis, date of study withdrawal, or last follow-up. For the main associations, average hours/week and MET-hours/week were considered both continuously and categorically. Categorically, hours/week was examined as 0–<1, 1–<4, 4–<7, ≥7 hours per week which were chosen *a priori* as interpretable cut-points for public health recommendations and to be comparable with another study in this population (32), while MET-hours/week were categorized in quartiles. Outcomes considered were overall breast cancer, with stratification by menopausal status, and invasive breast cancer stratified by estrogen receptor (ER) status. In the analyses of premenopausal breast cancer, women who transitioned from premenopausal to postmenopausal during follow-up were censored at the age of menopause. Person-time occurring after menopause contributed to postmenopausal risk time.

To assess effect-measure modification by family history risk score, an interaction term between the risk score and physical activity was used. Results are presented as a stratified analysis along with the ratio of stratified HRs and $P_{\text{interaction}}$ as measures of heterogeneity. To maintain sufficient study power to assess effect-measure modification, variables were classified as ≥7 versus <7 for hours/week, an interquartile range (IQR) increase for MET-hours/week, and ≥median versus <median for family history risk score. The modification analysis was conducted separately for pre- and postmenopausal breast cancer.

All models were adjusted for confounders selected using a directed acyclic graph (DAG; refs. 33, 34). The DAG-based minimally sufficient adjustment set included race (non-Hispanic white/non-Hispanic black/Hispanic/other), residence type (urban/suburban/small town/rural/other), education (<high school/high school equivalent/some college/≥ 4-year degree), parity (nulliparous/parous), alcohol use (never/past/current < 1 drink per day/current 1+ drink per day), and smoking status (never/past/current).

Primary results considered all breast cancer cases (ductal carcinoma *in situ* and invasive) combined, but we also considered whether results were similar for invasive cases alone. In a sensitivity analysis, we examined whether results changed when participants known to be carriers of the risk-related BRCA 1 or 2 mutations were excluded. Body mass index (BMI) could be considered a mediator of the physical activity–breast cancer associations, so it was not included in the adjustment set. However, due to its close relation and temporality with physical activity, it is possible that it could also serve as a confounder, so we conducted a sensitivity analysis adjusting for BMI at enrollment.

The proportional hazards assumption was evaluated by including an interaction term between the covariates and survival time. There were borderline violations of the proportional hazard assumption for the physical activity variables with overall breast cancer. This may have been due to heterogeneity by menopausal status because violations were not observed in analyses for postmenopausal breast cancer. Analyses were performed in SAS 9.4 (SAS Institute Inc.).

Results

During follow-up (average 8.4 years), 3,023 breast cancers were diagnosed among the 50,721 women. Characteristics of the study population stratified on hours/week of physical activity are shown in Table 1. Compared with those who did <1 hour/week of recreational physical activity, women who did ≥7 hours/week were slightly more likely to be non-Hispanic white, have a college degree or higher, be nulliparous, and currently consume ≥1 alcoholic drink/day.

Participation in ≥7 versus <1 hours/week of recreational physical activity (HR = 0.85; 95% CI, 0.74–0.98), as well as all quartiles of MET-hours/week above the referent (e.g., $HR_{\text{quartile4vs1}} = 0.83$; 95% CI, 0.75–0.92), was associated with a reduced overall breast cancer risk (Table 2). Additionally, regular participation in at least one activity in the past 12 months was inversely associated with overall breast cancer risk (HR = 0.89; 95% CI, 0.81–0.98). The inverse associations for hours/week, MET-hours/week, and at least one activity were all stronger for postmenopausal compared with overall breast cancer. In contrast, physical activity was suggestively associated with increased premenopausal breast cancer risk using all three metrics of physical activity. HRs were elevated for ≥7 versus <1 hours/week of physical activity (HR = 1.35; 95% CI, 0.96–1.89), the highest versus lowest quartile of MET-hours/week (HR = 1.25; 95% CI, 0.98–1.60), and performing at least one activity in the past 12 months (HR = 1.26; 95% CI, 0.98–1.62).

As for overall breast cancer, participation in ≥7 versus <1 hours/week was inversely associated with ER^+ invasive breast cancer (HR = 0.78; 95% CI, 0.65–0.94; Table 3). All quartiles of MET-hours/week above the referent were inversely associated with ER^+ breast cancer (e.g., $HR_{\text{quartile4vs1}} = 0.78$; 95% CI, 0.68–0.90). For ER^- invasive breast cancer (a much smaller category) the point estimates also were inverse, but not statistically significant, for both hours/week and MET-hours/week. Regular participation in at least one activity in the past 12 months was inversely associated with ER^+ invasive breast cancer (HR = 0.84; 95% CI, 0.74–0.95), but, conversely, had a suggestive positive association with ER^- breast cancer (HR = 1.18; 95% CI, 0.85–1.63).

Because of the heterogeneity in the main associations by menopausal status, we examined effect-measure modification by extent of family history for pre- and postmenopausal breast cancer separately (Table 4). Extent of family history did not appear to be a significant effect-measure modifier of the association between hours/week of physical activity and postmenopausal breast cancer (ratio of HRs = 1.14; 95% CI, 0.84–1.53; $P_{\text{interaction}} = 0.4$). The inverse association between ≥7 hours/week versus <7 hours/week of physical activity among those with family history risk score below the median (HR = 0.80; 95% CI, 0.64–0.99) was slightly attenuated among those with a family history risk score above the median (HR = 0.91; 95% CI, 0.74–1.11), but there was substantial overlap in the CIs. Further, an IQR increase in MET-hours/per week was associated with a decreased postmenopausal breast cancer risk regardless of whether family history risk score was above or below the median. Extent of family history also did not appear to modify the associations for either of the associations between

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Table 1. Characteristics of the study population by hours per week of physical activity, The Sister Study

	<1 hour per week $N = 17{,}192$ (33.9%) *N* (%)	1–6 hours per week $N = 29{,}046$ (57.3%) *N* (%)	≥7 hours per week $N = 4{,}438$ (8.8%) *N* (%)
Age at baseline (mean, SD)	54.9 (9.0)	55.8 (9.0)	57.3 (8.6)
Race/ethnicity			
Non-Hispanic white	13,601 (79.1)	24,897 (85.7)	3,892 (87.7)
Non-Hispanic black	1,890 (11.0)	2,284 (7.9)	274 (6.2)
Hispanic	1,197 (7.0)	1,162 (4.0)	144 (3.3)
Other	503 (2.9)	697 (2.4)	126 (2.8)
Missing	1 (–)	6 (–)	2 (–)
Highest level of education			
Less than high school	361 (2.1)	232 (0.8)	30 (0.7)
High school graduate	3,259 (19.0)	3,472 (12.0)	416 (9.4)
Some college	6,578 (38.3)	9,334 (32.1)	1,208 (27.2)
College degree or higher	6,993 (40.7)	16,004 (55.1)	2,783 (62.7)
Missing	1 (–)	4 (–)	1 (–)
Residence type			
Urban	3,325 (19.4)	5,635 (19.4)	908 (20.5)
Suburban	6,140 (35.8)	11,532 (39.7)	1,757 (39.7)
Small town	3,632 (21.2)	6,112 (21.1)	990 (22.4)
Rural	3,996 (23.3)	5,652 (19.5)	758 (17.1)
Other	54 (0.3)	73 (0.3)	16 (0.4)
Missing	45 (–)	42 (–)	9 (–)
Parity			
Nulliparous	2,825 (16.4)	5,332 (18.4)	1,017 (23.0)
Parous	14,361 (83.6)	23,694 (81.6)	3,413 (77.0)
Missing	6 (–)	20 (–)	8 (–)
Alcohol use			
Never	834 (4.9)	980 (3.4)	122 (2.8)
Former	3,357 (19.6)	3,792 (13.1)	550 (12.4)
Current, <1 drink/day	11,150 (65.0)	20,037 (69.1)	2,945 (66.5)
Current, 1+ drink/day	1,822 (10.6)	4,202 (14.5)	811 (18.3)
Missing	29 (–)	35 (–)	10 (–)
Smoking status			
Never	9,511 (55.3)	16,490 (56.8)	2,451 (55.2)
Past	5,557 (32.3)	10,741 (37.0)	1,763 (39.7)
Current	2,123 (12.4)	1,811 (6.2)	224 (5.1)
Missing	1 (–)	4 (–)	0 (–)

hours/week or MET-hours/week of physical activity and premenopausal breast cancer risk. Although based on small numbers, the positive association between ≥7 hours/week and premenopausal breast cancer was seen only among those with above the median family history score (ratio of the HRs = 1.72; 95% CI, 0.73–4.02; $P_{\text{interaction}} = 0.2$). Similarly, there was a positive association for an IQR increase in MET-hours/week (HR = 1.10; 95% CI, 1.02–1.19) among those with a family history risk score above the median and no association among those with a family history risk score below the median (HR = 1.02; 95% CI,

Table 2. HRs and 95% CIs for the associations between physical activity and breast cancer risk, The Sister Study

		Overall		Premenopausal		Postmenopausal	
	PY	*N* cases	HR[a,b] (95% CI)	*N* cases	HR[a] (95% CI)	*N* cases	HR[a] (95% CI)
Total average hours/week							
Continuous	421,807	3,017	0.99 (0.97–1.00)	533	1.03 (1.00–1.06)	2,460	0.98 (0.96–0.99)
0–<1	140,497	1,035	1.00	170	1.00	859	1.00
1–<4	173,872	1,220	0.91 (0.84–0.99)	225	1.13 (0.92–1.38)	983	0.87 (0.79–0.95)
4–<7	70,425	506	0.90 (0.81–1.01)	95	1.29 (1.00–1.66)	408	0.83 (0.74–0.94)
≥7	37,013	256	0.85 (0.74–0.98)	43	1.35 (0.96–1.89)	210	0.77 (0.66–0.90)
Total average MET-hours/week							
Continuous (IQR increase)	421,807	3,017	0.97 (0.93–1.00)	533	1.08 (1.01–1.16)	2,460	0.92 (0.89–0.97)
Quartile 1	102,481	791	1.00	121	1.00	666	1.00
Quartile 2	110,532	753	0.86 (0.78–0.95)	131	0.99 (0.77–1.27)	616	0.83 (0.74–0.93)
Quartile 3	101,971	736	0.88 (0.79–0.97)	126	1.14 (0.88–1.47)	602	0.83 (0.74–0.92)
Quartile 4	106,822	737	0.83 (0.75–0.92)	155	1.25 (0.98–1.60)	576	0.75 (0.67–0.85)
At least one activity in the past 12 months							
No	69,105	524	1.00	73	1.00	449	1.00
Yes	352,943	2,493	0.89 (0.81–0.98)	460	1.26 (0.98–1.62)	2,011	0.82 (0.74–0.91)

Abbreviations: PY, person-years.
[a]Adjusted for race, residence type, education, parity, alcohol use, and smoking status.
[b]Borderline violation of proportional hazards assumption.

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Table 3. HRs and 95% CIs for the associations between hours/week of physical activity and breast cancer risk by invasive ER status, The Sister Study

	ER$^-$		ER$^+$	
	***N* cases**	**HR[a] (95% CI)**	***N* cases**	**HR[a] (95% CI)**
Total average hours/week				
Continuous	304	0.98 (0.94–1.02)	1,733	0.98 (0.97–1.00)
0–<1	105	1.00	599	1.00
1–<4	134	1.06 (0.82–1.37)	696	0.87 (0.78–0.97)
4–<7	42	0.82 (0.57–1.18)	294	0.86 (0.75–1.00)
≥7	23	0.85 (0.54–1.35)	144	0.78 (0.65–0.94)
Total average MET-hours/week				
Continuous (IQR increase)	304	0.97 (0.86–1.09)	1,733	0.94 (0.89–0.99)
Quartile 1	79	1.00	455	1.00
Quartile 2	71	0.86 (0.62–1.18)	429	0.83 (0.73–0.95)
Quartile 3	91	1.20 (0.88–1.63)	429	0.85 (0.74–0.97)
Quartile 4	63	0.80 (0.57–1.12)	420	0.78 (0.68–0.90)
At least one activity in the past 12 months				
No	45	1.00	306	1.00
Yes	259	1.18 (0.85–1.63)	1,427	0.84 (0.74–0.95)

Abbreviations: −, negative; +, positive.
[a]Adjusted for race, residence type, education, parity, alcohol use, and smoking status.

0.86–1.20); however, there was substantial overlap in the CIs (ratio of the HRs = 1.08; 95% CI, 0.90–1.31; $P_{\text{interaction}} = 0.5$).

In sensitivity analyses, results were similar when restricted to invasive cases only (Supplementary Tables S1 and S2), when participants known to be BRCA 1 or 2 mutation carriers were excluded (Supplementary Tables S3 and S4), and with BMI adjustment (Supplementary Tables S5 and S6).

Discussion

We observed an inverse association between adulthood recreational physical activity in the previous 12 months and overall breast cancer risk in a large prospective cohort of women with a family history of breast cancer. This result is consistent with the established inverse association between physical activity and breast cancer without considering family history (1, 2). Inverse associations for physical activity were also found for ER$^+$ invasive breast cancer and for postmenopausal breast cancer. In contrast, there was a suggestive positive association between physical activity and premenopausal breast cancer in this population.

To our knowledge, this is the first study to date that has evaluated the association between physical activity and breast cancer in a large population of women with a family history of breast cancer. However, some studies have compared physical activity–associated risks for women with or without at least one first-degree female relative with breast cancer, with inconsistent results. Two studies found that although there was an inverse association between physical activity and breast cancer in both those with and without a family history, the association was stronger among those with a family history (9, 10). In six studies, it was reported that there was no difference in the association between those with and without a family history (11–16). In seven studies, the association was stronger in those without a family history or, in contrast to our results, there was no association between physical activity and breast cancer among those with a family history of breast cancer (17–23). The discrepancies among the studies to date may be due to sample size limitations. In the previous studies, only a small percentage (5.3%–16.6%) of the population had a family history of breast cancer, often resulting in small numbers in categories of physical activity and limited exploration of the extent of family history. As a result, drawing conclusions about whether physical activity reduces the risk of breast cancer in women with a family history has been difficult. The study reported here makes an important contribution by investigating this question in a large sample with a family history of breast cancer, leading to more precise estimates of the association between physical activity and breast cancer.

Table 4. Evaluation of effect-measure modification by family history score for the associations between physical activity and breast cancer incidence, by menopausal status, The Sister Study

Family history score	Physical activity	*N* cases	Stratified HR[a] (95% CI)	Ratio of stratified HRs	*P*
Postmenopausal					
Low (<median)	<7 hours/week	987	1.00		
	≥7 hours/week	90	0.80 (0.64–0.99)		
High (≥median)	<7 hours/week	1,043	1.00		
	≥7 hours/week	98	0.91 (0.74–1.11)	1.14 (0.84–1.53)	0.4
Low (<median)	IQR increase in MET-hours/week	1,077	0.95 (0.88–1.01)		
High (≥median)	IQR increase in MET-hours/week	1,141	0.92 (0.86–0.98)	0.97 (0.88–1.07)	0.6
Premenopausal					
Low (<median)	<7 hours/week	108	1.00		
	≥7 hours/week	7	0.78 (0.36–1.68)		
High (≥median)	<7 hours/week	333	1.00		
	≥7 hours/week	31	1.34 (0.93–1.94)	1.72 (0.73–4.02)	0.2
Low (<median)	IQR increase in MET-hours/week	115	1.02 (0.86–1.20)		
High (≥median)	IQR increase in MET-hours/week	364	1.10 (1.02–1.19)	1.08 (0.90–1.31)	0.4

[a]Adjusted for race, residence type, education, parity, alcohol use, and smoking status.

Biological mechanisms support the plausibility of inverse associations between physical activity and overall and postmenopausal breast cancer risk, as has been discussed previously (35–37). Briefly, physical activity reduces circulating levels and cumulative exposure to sex hormones, can lead to weight loss/maintenance (particularly important for reducing breast cancer risk in postmenopausal women when the main source of estrogen is from adipose tissue; ref. 35), and can improve insulin sensitivity and lower circulating insulin levels (38–40), all factors that can influence breast carcinogenesis (35–37).

Women with a family history of breast cancer have been shown to have higher levels of estrone/estradiol compared with women without a family history (41, 42), which suggests it may be important to examine the association for physical activity, a factor that operates through a hormonal pathway, among women with a family history of breast cancer (18) and examine extent of that family history as a modifier. Given that we observed inverse associations between physical activity and overall, ER^+, and postmenopausal breast cancer risk in women with a family history, consistent with the literature on physical activity and breast cancer risk in the general population, it is possible that physical activity may lower estrogen levels sufficiently to negate the possible hormonal differences between those with and without a family history of breast cancer, and regardless of the extent of the family history in postmenopausal women.

We observed a suggestive positive association between physical activity and premenopausal breast cancer risk, which is in contrast to a meta-analysis that reported a RR of 0.80 (95% CI, 0.74–0.87) for premenopausal breast cancer (26). Although slightly attenuated, the suggestive positive association in our study was maintained even with additional adjustment for BMI, which is inversely associated with breast cancer in premenopausal women (43). Further, the positive association with premenopausal breast cancer was suggestively more apparent in women with a higher family history score. Prior studies of physical activity and premenopausal breast cancer used populations with only a small proportion of women who had family history of breast cancer. It is possible that our result reflects a true difference among women that have a family history of breast cancer, which is supported by the stronger associations for those with a higher risk score. A previous study found that although family history is associated with an increased risk of breast cancer at all ages, the magnitude of association is stronger among premenopausal women, especially at younger ages (44). Further, family history of breast cancer may reflect shared lifestyle risk factors as well as genetic risk. Among women who are younger and in premenopausal years, it is conceivable that family history may imply a stronger baseline risk or a larger genetic influence than physical activity can overcome.

The Sister Study was conducted with a prospective design where the baseline interview assessing physical activity was completed before women were diagnosed with breast cancer. As a result, differential recall bias between those with and without breast cancer was not a possibility in our study. This study was also strengthened by a large sample size which resulted in precise CIs for the main associations and allowed for sufficient power to examine modification. Additionally, we examined physical activity classified in multiple ways: at least one activity, hours/week, and MET-hours/week. It was reassuring that results were consistent across all measures of physical activity in our study. Finally, this was the first study to utilize a novel family history risk score that is more accurate than "yes/no" or 0/1/1+ first-degree female relative classifications because it accounts for the age/sex structure of the family and diagnoses.

We relied on self-report of sport/exercise activities in the 12 months before enrollment. We cannot exclude the possibility of nondifferential exposure misclassification based on the ability to accurately recall activities. However, a study on the validity and reproducibility of a physical activity questionnaire that, similar to ours, asked women to report what activities they did during the past year along with the duration and frequency to determine hours/week and MET-hours/week concluded that the physical activity questionnaire was highly reproducible over a 1-year period (45). This lessens the concerns about recall of activities in our study. Women were asked about only activities they participated in during the past 12 months, so one of the assumptions of our study is that this is reflective of their longer-term behavior that would be relevant for the lengthy induction period of breast cancer. As follow-up data on recreational physical activity were obtained using a different approach, we could not account for changes in physical activity during the follow-up period, which could lead to some misclassification of exposure. In this study, we focused on recreational physical activity and did not include other types such as occupational or household physical activity. Although meta-analyses found similar risk reductions for both occupational versus nonoccupational physical activity (1, 2) and recreational versus household physical activity (1), we cannot exclude the possibility that results for total activity (summed across all types) or occupational/household activity alone could have differed. The physical activity assessment in a few other studies captured hours/week of moderate-to-vigorous activities only, whereas our study asked women to report all recreational sport/exercise activities. There is likely misclassification with either approach. It is possible that our estimates of the beneficial effects are attenuated compared with what we would have observed if we had focused on only moderate-to-vigorous physical activities. However, by including all sport/exercise activities, our assessment is a closer reflection of a woman's total recreational physical activity level over the past year. Finally, there were fewer ER^- cancers and premenopausal women in this population, despite the large overall sample size. As a result, the estimates were less precise in these subgroups.

In summary, we found that among women with a first-degree family history of breast cancer, physical activity reduced overall, ER^+, and postmenopausal breast cancer risk, although not premenopausal breast cancer. Beyond having a family history, extent of that family history did not appear to modify the associations of physical activity with postmenopausal breast cancer risk. Physical activity was beneficial regardless of whether a woman had a family history risk score above or below the median. Among premenopausal women, although there was no significant modification by extent of family history, the associations were suggestive of increased risk only among those with a stronger family history.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: N.M. Niehoff, A.J. White, D.P. Sandler
Development of methodology: N.M. Niehoff, S. Zhao, D.P. Sandler

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D.P. Sandler
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N.M. Niehoff, H.B. Nichols, S. Zhao, A.J. White, D.P. Sandler
Writing, review, and/or revision of the manuscript: N.M. Niehoff, H.B. Nichols, S. Zhao, A.J. White, D.P. Sandler
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N.M. Niehoff
Study supervision: D.P. Sandler

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