Physical Activity and Postmenopausal Breast Cancer Risk in the NIH-AARP Diet and Health Study

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Abstract

Background: **Although physical activity has been associated with reduced breast cancer risk, whether this association varies across breast cancer subtypes or is modified by reproductive and lifestyle factors is unclear.**

Methods: **We examined physical activity in relation to postmenopausal breast cancer risk in 182,862 U.S. women in the NIH-AARP Diet and Health Study. Physical activity was assessed by self-report at baseline (1995-1996), and 6,609 incident breast cancers were identified through December 31, 2003. Cox regression was used to estimate the relative risk (RR) and 95% confidence interval (95% CI) of postmenopausal breast cancer overall and by tumor characteristics. Effect modification by select reproductive and lifestyle factors was also explored.**

Results: **In multivariate models, the most active women experienced a 13% lower breast cancer risk versus inactive women (RR, 0.87; 95% CI, 0.81-0.95). This inverse relation was not modified by tumor stage or histology but was suggestively stronger for estrogen receptor (ER)-negative (RR, 0.75; 95% CI, 0.54-1.04) than ER-positive (RR, 0.97; 95% CI, 0.84-1.12) breast tumors and was suggestively stronger for overweight/obese (RR, 0.86; 95% CI, 0.77-0.96) than lean (RR, 0.95; 95% CI, 0.87-1.05) women. The inverse relation with physical activity was also more pronounced among women who had never used menopausal hormone therapy and those with a positive family history of breast cancer than their respective counterparts.**

Conclusions: **Physical activity was associated with reduced postmenopausal breast cancer risk, particular to ER-negative tumors. These results, along with heterogeneity in the physical activity-breast cancer relation for subgroups of menopausal hormone therapy use and adiposity, indicate that physical activity likely influences breast cancer risk via both estrogenic and estrogen-independent mechanisms.** (Cancer Epidemiol Biomarkers Prev 2009;18(1):289–96)

Introduction

Breast cancer is the most common cancer among women in the United States, and an estimated 182,000 new cases will be diagnosed in the United States in 2008 (1). Although certain risk factors for postmenopausal breast cancer such as genetic predisposition, age, and reproductive history are nonmodifiable, several lifestyle and behavioral characteristics are also related to risk. High levels of physical activity have been consistently associated with reduced risk of postmenopausal breast cancer independent of body size. The magnitude of this inverse association ranges from 20% to 80% across studies, with most investigations estimating 20% to 40% reduced risk (2-5), and a recent review reported similar risk reductions for both moderate and vigorous (average 22% and 26% reduced risk, respectively) physical activity (5).

Despite the accumulated evidence that an active lifestyle lowers breast cancer risk, the precise mechanism by which physical activity influences tumor development

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Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health.

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is unknown. As postmenopausal breast cancer is associated with high estrogen levels (6), one hypothesis involves a reduction in levels of endogenous sex hormones (7). Other estrogen-independent pathways have also been proposed, including an effect of activity in modulating levels of insulin and insulin-like growth factors, enhancing immunity, and reducing chronic inflammation (8).

The plausibility of these mechanisms could be further informed by examining modification of the association between physical activity and breast cancer risk by estrogen-related factors and by breast tumor characteristics such as estrogen receptor (ER) and progesterone receptor (PR) status, tumor stage, and histology. Reports that the relation of estrogen-related factors such as parity, age at first birth, age at menarche, and postmenopausal adiposity to risk varies across breast tumor subtypes (9-11) support the idea that breast cancer subtypes represent distinct diseases with respective etiologies and prognoses (12). However, it remains unclear whether the association between physical activity and breast cancer differs by tumor characteristics. Within the large, prospective NIH-AARP Diet and Health Study, we evaluated the association between physical activity and postmenopausal breast cancer risk overall and by ER and PR status, tumor stage, and histology. We also examined effect modification by select lifestyle and reproductive factors.

Materials and Methods

Study Population. The NIH-AARP Diet and Health Study has been described previously (13). Briefly, between the years 1995 and 1996, members of the American Association of Retired Persons residing in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or two urban areas (Atlanta, GA, and Detroit, MI) were recruited to the study. A baseline questionnaire to assess diet, physical activity, and medical history was mailed to 3.5 million American Association of Retired Persons members and was satisfactorily completed by 566,402 individuals ages 50 to 71 years, of whom 241,228 were women. A second questionnaire distributed within 6 months of the baseline questionnaire was used to obtain additional information on histories of mammography and benign breast disease.

After excluding premenopausal women (n = 7,249) and those with unknown menopausal status (n = 1,883), women with prevalent cancers (other than nonmelanoma skin cancer; n = 23,957), those with questionnaires completed by proxy (n = 15,760), and those with missing or extreme values of height, weight, or physical activity (n = 9,517), 182,862 postmenopausal women remained for analysis. Postmenopausal status was defined as report of either natural menopause, bilateral oophorectomy, hysterectomy, or age $\geq$57 years. Extreme values were defined by the Box-Cox transformation. The Special Studies Institutional Review Board of the National Cancer Institute approved this study, and completion of the self-administered baseline questionnaire was considered to imply informed consent.

Cohort Follow-up and Case Ascertainment. Cohort members were followed for change of address via annual linkage to the National Change of Address database maintained by the U.S. Postal Service, by notifications of undelivered mail, through other address update services, and by direct notice from participants. Vital status was ascertained by annual linkage to the Social Security Administration Death Master File, and searches of the National Death Index Plus were used to verify vital status and to provide cause of death information.

Incident breast cancer cases were identified by linkage to 11 state cancer registries (including the addition of Texas, Arizona, and Nevada to the eight states in which baseline data were collected). Hormone receptor status was available from 7 (California, Louisiana, Georgia, North Carolina, New Jersey, Arizona, and Nevada) of the 11 reporting states, with a positive hormone receptor status recorded at a threshold of at least 10 fmol receptor/mg total protein. Although hormone receptor data were unavailable for cases from Florida, Pennsylvania, Michigan, and Texas, the distribution of risk factors considered in our study was similar for women from states with and without hormone receptor information (data not shown); thus, noncases from these states were included in analyses. Sensitivity analyses confirmed that results were unchanged when including as noncases only women from states where ER status was known.

The *International Classification of Diseases for Oncology, Third Edition* coding system was used to classify tumor histology, with ductal cases defined by code 8500 or 8523, lobular cases by code 8520 or 8524, and tumors of mixed histology by code 8522. The completeness of case ascertainment in our cohort has been reported previously, with an estimated sensitivity of ~90% and specificity of 99.5% with respect to identification of cases by cancer registry linkage (14).

Physical Activity Assessment. Physical activity was assessed in the baseline questionnaire by asking participants to report the frequency over the past year of ''activities at work or home, including exercise, sports, and activities such as carrying heavy loads. . .which lasted at least 20 minutes, and caused increases in breathing or heart rate, or caused you to work up a sweat.'' Participants were classified into one of five activity categories: inactive; active less than once per week; active 1 to 2 times per week; active 3 to 4 times per week; and active $\geq$5 times per week. The questionnaire used was similar to an instrument that has been validated using objective methods (percentage agreement = 0.71; ref. 15).

Statistical Analysis. Cox proportional hazards regression with age as the time metric was used to estimate the relative risk (RR) of postmenopausal breast cancer. We tested and confirmed that the proportionality assumption was not violated. Follow-up time was calculated from the scan date of the baseline questionnaire through the date of diagnosis of breast cancer or other cancer (except nonmelanoma skin cancer), death, or the end of the study on December 31, 2003. Models were adjusted for potential confounding variables (Table 1). Analyses were done with and without inclusion of body mass index (BMI) as a covariate, because BMI could mediate the association between physical activity and breast cancer risk.

Table 1. Characteristics of the study population by level of physical activity at baseline, 182,862 postmenopausal women, NIH-American Association of Retired Persons Diet and Health Study (1995-1996)

Characteristics	Total	Physical activity (times per week)				
		Inactive	<1	1-2	3-4	≥5
Participants, *n* (%)	182,862	41,580 (22.7)	26,311 (14.4)	38,713 (21.2)	46,251 (25.3)	30,007 (16.4)
Age at baseline (y)	62.1	62.4	61.3	61.8	62.4	62.5
BMI (kg/m^2)	26.9	28.6	27.6	26.9	26.0	25.3
Race/ethnicity (%)						
White	89.9	88.5	90.2	90.6	90.0	90.8
Black	5.5	6.6	5.6	5.0	5.3	4.9
Hispanic	1.9	2.3	1.8	1.8	1.9	1.5
Asian/Pacific Islander/Native American	1.5	1.4	1.3	1.5	1.7	1.6
College education (%)	29.6	21.6	28.5	31.0	33.1	34.2
Family history of breast cancer* (%)	12.4	12.0	12.6	12.5	12.5	12.4
Current smoker (%)	14.4	19.7	17.6	14.8	10.6	9.6
Current MHT use (%)	44.9	37.8	45.3	46.0	48.9	47.0
Age at menarche (y)	12.51	12.46	12.48	12.50	12.53	12.55
Age at first birth in parous women (y)	22.88	22.68	22.78	22.94	23.02	22.97
Parity (no. children)	2.01	2.02	2.01	2.00	2.02	1.99
Age at menopause (y)	46.88	46.46	46.76	46.91	47.11	47.21
Alcohol intake (g/d)	6.0	5.8	6.1	5.8	6.1	6.3
Total energy intake† (kcal/d)	1,597.4	1,623.5	1,557.3	1,583.2	1,576.1	1,647.4

NOTE: All values, except age, are adjusted for age.
*Family history of breast cancer in a first-degree female relative.
†Adjusted for total energy intake.

In the subgroup of women who completed the second questionnaire (n = 116,159), we investigated potential confounding of the physical activity-breast cancer association by mammogram history during the preceding 3 years and by previous benign breast disease.

Interaction was explored by likelihood ratio tests comparing models with and without interaction terms. As interaction tests were not sensitive to adjustment for BMI, results are presented without inclusion of BMI in statistical models. Physical activity was modeled as an ordinal variable in all interaction tests and tests of linear trend.

In separate analyses, we investigated the relation of physical activity to distinct endpoints: ER/PR status (ER− or ER+ tumors; ER+/PR+, ER+/PR−, ER−/PR+, ER−/PR−, or unknown ER/PR tumors), tumor stage (invasive or *in situ* breast cancer; localized or regional/distant breast cancer), and histologic subtype (ductal, lobular, or mixed histology). Analyses of hormone receptor status and tumor histology were restricted to invasive cancers. Unknown ER/PR tumors (n = 3039) included borderline, missing, and unknown hormone receptor status. Heterogeneity by the above tumor characteristics was evaluated by comparison of the test of trend for each outcome using Cochran's Q statistic (16).

Analyses were done using SAS (version 9.1; SAS Institute), with all statistical tests two-sided and conducted at the 0.05 significance level.

Results

During an average of 7 years of follow-up, 6,609 cases of incident breast cancer were ascertained, including 1,176 (17.8%) *in situ* cancers. Women were an average age of 62.1 years at baseline, and 22.7% were categorized as inactive (Table 1). The majority of participants (~90%) were Caucasian, and ~30% were college educated. The most active women were more likely than the total cohort to be college educated, to report current menopausal hormone therapy (MHT) use, and to drink alcohol, and were less likely to be current smokers. BMI decreased with increasing physical activity, and women active ≥5

Table 2. RR (95% CI) for the association between physical activity and postmenopausal breast cancer incidence among 182,862 postmenopausal women

Physical activity (times per week)	Person-years	No. cases	Age-adjusted RR (95% CI)	Multivariate RR* (95% CI)	Multivariate RR† (95% CI)
Inactive	285,349	1,485	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
<1	184,682	981	1.04 (0.96-1.13)	0.99 (0.91-1.07)	1.00 (0.92-1.08)
1-2	271,497	1,391	0.99 (0.92-1.07)	0.94 (0.87-1.01)	0.96 (0.89-1.03)
3-4	325,701	1,711	1.01 (0.94-1.08)	0.93 (0.87-1.00)	0.97 (0.90-1.04)
≥5	211,557	1,041	0.94 (0.87-1.02)	0.87 (0.81-0.95)	0.92 (0.85-1.00)
P_{trend}			0.13	<0.001	0.04

*Multivariate models used age as the underlying time metric and were adjusted for race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander/American Indian), education level (<12 years or high school equivalent, 12 years or high school equivalent, post-high school vocational or technical training, some college, college graduate, postgraduate), smoking status (nonsmoker, former, current), family history of breast cancer (no, yes), menopausal hormone use (never, current, past), age at first birth (nulliparous, <20, 20-24, 25-29, ≥30 years), age at menarche (<13, 13-14, ≥15 years), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 years), parity (number of children: 0, 1-2, ≥3), and alcohol intake (g/d; quintiles adjusted for total energy intake).
†Additionally adjusted for BMI (<25.0, 25.0-29.9, 30.0-34.9, ≥35.0 kg/m^2).

Table 3. Multivariate RR (95% CI) for the association between physical activity and breast cancer incidence among postmenopausal women according to selected tumor characteristics

Tumor characteristics*	No. cases	Physical activity (times per week)					P_{trend}	$P_{heterogeneity}$
		Inactive	<1	1-2	3-4	≥5		
Hormone receptor status								
ER+	2,083	1.0 (Reference)	1.03 (0.89-1.19)	0.95 (0.83-1.08)	0.98 (0.86-1.11)	0.97 (0.84-1.12)	0.64	0.07
ER−	411	1.0 (Reference)	1.10 (0.81-1.49)	0.85 (0.63-1.14)	0.85 (0.64-1.12)	0.75 (0.54-1.04)	0.03	
ER+/PR+	1,649	1.0 (Reference)	1.00 (0.84-1.18)	0.97 (0.84-1.13)	0.96 (0.83-1.11)	0.96 (0.82-1.13)	0.53	
ER+/PR−	338	1.0 (Reference)	1.29 (0.90-1.84)	0.93 (0.65-1.32)	1.17 (0.85-1.60)	1.05 (0.73-1.51)	0.85	
ER−/PR+	48	1.0 (Reference)	1.10 (0.41-2.95)	1.15 (0.47-2.78)	1.29 (0.56-2.95)	0.62 (0.21-1.86)	0.56	0.37
ER−/PR−	359	1.0 (Reference)	1.10 (0.80-1.53)	0.84 (0.61-1.15)	0.81 (0.60-1.10)	0.78 (0.55-1.10)	0.05	
Unknown ER or PR	3,039	1.0 (Reference)	0.90 (0.80-1.02)	0.95 (0.85-1.06)	0.92 (0.83-1.01)	0.81 (0.72-0.91)	0.002	
Tumor stage								
In situ	1,176	1.0 (Reference)	1.10 (0.91-1.33)	0.90 (0.75-1.08)	0.93 (0.78-1.10)	0.93 (0.77-1.13)	0.20	0.85
Invasive	5,433	1.0 (Reference)	0.97 (0.88-1.06)	0.95 (0.87-1.03)	0.94 (0.87-1.01)	0.86 (0.79-0.94)	0.001	
Localized	3,158	1.0 (Reference)	0.97 (0.86-1.09)	0.95 (0.86-1.06)	1.00 (0.90-1.10)	0.85 (0.76-0.96)	0.04	0.17
Regional/distant	1,298	1.0 (Reference)	0.99 (0.83-1.17)	0.83 (0.71-0.98)	0.74 (0.63-0.86)	0.85 (0.71-1.01)	0.003	0.36 †
Tumor histology								
Ductal	3,568	1.0 (Reference)	0.98 (0.88-1.10)	0.96 (0.87-1.06)	0.93 (0.84-1.02)	0.89 (0.80-0.99)	0.02	
Lobular	550	1.0 (Reference)	1.24 (0.95-1.63)	0.92 (0.71-1.19)	0.89 (0.69-1.14)	0.87 (0.65-1.15)	0.05	0.41
Ductal-lobular	436	1.0 (Reference)	0.80 (0.58-1.12)	0.80 (0.60-1.08)	0.95 (0.73-1.24)	0.89 (0.66-1.20)	0.96	

NOTE: Multivariate models used age as the underlying time metric and were adjusted for race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander/American Indian), education level (<12 years or high school equivalent, 12 years or high school equivalent, post-high school vocational or technical training, some college, college graduate, postgraduate), smoking status (nonsmoker, former, current), family history of breast cancer (no, yes), menopausal hormone use (never, current, past), age at first birth (nulliparous, <20, 20-24, 25-29, ≥30 years), age at menarche (<13, 13-14, ≥15 years), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 years), parity (number of children: 0, 1-2, ≥3), and alcohol intake (g/d; quintiles adjusted for total energy intake).
*Hormone receptor status and tumor histology limited to invasive cancers.
†*P* value for comparison of *in situ*, localized, and regional/distant.

times per week had the lowest average BMI despite greater total energy consumption.

Similar to previous reports (17), women diagnosed with incident breast cancer were more likely to have a first-degree female relative with breast cancer and to experience an earlier age at menarche, later age at first birth, reduced parity, later age at menopause, greater MHT use, slightly higher BMI, and increased alcohol intake relative to noncases (data not shown).

In age-adjusted models, physical activity was not statistically significantly associated with breast cancer (Table 2). However, after multivariate adjustment, the most active women experienced a 13% reduced breast cancer risk [RR, 0.87; 95% confidence interval (95% CI), 0.81-0.95] compared with inactive women. First-degree family history of breast cancer and MHT use accounted for the majority of the difference in risk estimates between age-adjusted and multivariate analyses, and the inverse relation was slightly attenuated after adding BMI to the model (RR, 0.92; 95% CI, 0.85-1.00).

Risk estimates were not sensitive to exclusion of the first 2 years of follow-up, to exclusion of women with a history of heart disease, or to adjustment for history of mammography or benign breast disease (data not shown).

Table 4. Multivariate RR (95% CI) for the association between physical activity and breast cancer incidence among postmenopausal women according to BMI, MHT use, and family history of breast cancer

	No. cases	Physical activity (times per week)					P_{trend}	$P_{heterogeneity}$
		Inactive	<1	1-2	3-4	≥5		
BMI (kg/m^2)								
≥25.0	3,787	1.0 (Reference)	0.98 (0.89-1.08)	0.98 (0.90-1.08)	0.92 (0.84-1.01)	0.86 (0.77-0.96)	0.003	0.07
<25.0	2,822	1.0 (Reference)	1.01 (0.92-1.11)	0.97 (0.89-1.05)	0.99 (0.92-1.08)	0.95 (0.87-1.05)	0.64	
MHT use								
Ever use	4,073	1.0 (Reference)	1.03 (0.93-1.15)	1.00 (0.90-1.10)	1.00 (0.92-1.10)	0.97 (0.88-1.08)	0.34	0.002
Never use	2,528	1.0 (Reference)	0.95 (0.84-1.08)	0.88 (0.79-0.99)	0.86 (0.77-0.96)	0.76 (0.67-0.86)	<0.001	
Family history								
Family history	1,193	1.0 (Reference)	0.99 (0.83-1.19)	0.92 (0.78-1.08)	0.75 (0.64-0.89)	0.75 (0.62-0.91)	<0.001	0.003
No family history	5,124	1.0 (Reference)	0.99 (0.90-1.09)	0.95 (0.87-1.03)	0.98 (0.90-1.06)	0.88 (0.81-0.97)	0.03	

NOTE: Multivariate models used age as the underlying time metric and were adjusted for race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander/American Indian), education level (<12 years or high school equivalent, 12 years or high school equivalent, post-high school vocational or technical training, some college, college graduate, postgraduate), smoking status (nonsmoker, former, current), family history of breast cancer (no, yes), menopausal hormone use (never, current, past), age at first birth (nulliparous, <20, 20-24, 25-29, ≥30 years), age at menarche (<13, 13-14, ≥15 years), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 years), parity (number of children: 0, 1-2, ≥3), and alcohol intake (g/d; quintiles adjusted for total energy intake).

The physical activity-breast cancer relation appeared to differ by ER status ($P_{heterogeneity}$ = 0.07). Women in the highest versus lowest category of activity displayed a borderline statistically significant 25% lower RR of ER− tumors (RR, 0.75; 95% CI, 0.54-1.04; Table 3). In contrast, no relation was seen with ER+ breast cancers (RR, 0.97; 95% CI, 0.84-1.12). Considering joint ER/PR status, the most active women showed statistically nonsignificant reductions in ER−/PR− and ER−/PR+ breast cancer risk compared with inactive women. However, no associations were evident for ER+/PR+ or ER+/PR− breast cancers.

No statistically significant heterogeneity was observed in the relation of physical activity to breast cancer tumor characteristics (Table 3). Whereas the association with physical activity appeared weak for the small subset of *in situ* breast cancers (RR for the most active versus inactive women, 0.93; 95% CI, 0.77-1.13), inverse relations were of similar magnitude for both localized tumors (RR, 0.85; 95% CI, 0.76-0.96) and tumors with regional/distant metastases (RR, 0.85; 95% CI, 0.71-1.01). Likewise, inverse relations with physical activity were comparable for ductal (RR, 0.89; 95% CI, 0.80-0.99), lobular (RR, 0.87; 95% CI, 0.65-1.15), and mixed ductal-lobular (RR, 0.89; 95% CI, 0.66-1.20) tumors.

The relation of physical activity to breast cancer risk was suggestively modified by BMI ($P_{heterogeneity}$ = 0.07) and appeared stronger for overweight and obese women (BMI ≥25 kg/m^2) than lean women (BMI <25 kg/m^2; Table 4). MHT use statistically significantly modified the relation of physical activity to breast cancer risk ($P_{heterogeneity}$ = 0.002), so that the inverse association was more pronounced among women with no history of MHT use than those with a history of MHT use (Table 4). The association between physical activity and breast cancer was also more apparent among women with a first-degree family history of breast cancer than those without a family history ($P_{heterogeneity}$ = 0.003; Table 4).

We also reevaluated the aforementioned associations after jointly classifying exposures and including a common reference group to obtain an estimate of overall risk (Table 5). Compared with overweight or obese women who were categorized as inactive, the RR of breast cancer for the subgroup of women who were both lean and engaged in physical activity ≥5 times per week was 0.80 (95% CI, 0.72-0.88). Using women with the combination of a positive family history of breast cancer and physical inactivity as the reference group, risk reduction for women who had no family history of breast cancer and were highly physically active was nearly 50% (RR, 0.51; 95% CI, 0.44-0.58). Substantial risk reduction was also observed for women with the combination of never MHT use and high physical activity level (RR, 0.60; 95% CI, 0.53-0.68) relative to women who used MHT and were physically inactive.

The physical activity-breast cancer association was not modified by age, race, education level, age at menarche, age at first birth, parity, age at menopause, cigarette smoking, history of mammography or benign breast disease, or alcohol intake (all $P_{heterogeneity}$ > 0.10; data not shown).

Discussion

In this large, prospective study, we report a modest but statistically significant reduction in the risk of postmenopausal breast cancer with a high versus low level of physical activity. Women active ≥5 times per week displayed a 13% reduced breast cancer risk compared with inactive women. This relation persisted across tumor stage and select histologic subtypes. In particular, the inverse association appeared more pronounced for ER− breast cancers, for overweight and obese women, for those who never used MHT, and for women with a history of breast cancer in a first-degree female relative. These findings add to the current literature supporting the notion that physical activity influences the risk of this common and deleterious disease (2-4).

Our observation that a high level of activity is specifically associated with a borderline significant reduction in ER− breast cancer risk distinguishes our study from prior investigations. The majority of previous evidence supporting an association between physical activity and postmenopausal breast cancer incidence is based primarily on ER+ tumors, which account for a substantial proportion of postmenopausal breast cancers (18).

Table 5. Multivariate RR (95% CI) for the association between physical activity and breast cancer incidence among postmenopausal women according to joint effect of physical activity and BMI, joint effect of physical activity and MHT use, and joint effect of physical activity and family history of breast cancer

	No. cases	Physical activity (times per week)				
		Inactive	<1	1-2	3-4	≥5
BMI (kg/m^2)						
≥25.0	3,787	1.0 (Reference)	0.98 (0.89-1.08)	0.98 (0.90-1.08)	0.92 (0.84-1.01)	0.86 (0.77-0.96)
<25.0	2,822	0.84 (0.75-0.94)	0.85 (0.75-0.96)	0.76 (0.68-0.84)	0.84 (0.77-0.92)	0.80 (0.72-0.88)
MHT use						
Ever use	4,073	1.0 (Reference)	1.03 (0.93-1.15)	1.00 (0.90-1.10)	1.01 (0.92-1.10)	0.97 (0.88-1.08)
Never use	2,528	0.79 (0.72-0.88)	0.76 (0.67-0.85)	0.70 (0.63-0.78)	0.68 (0.61-0.76)	0.60 (0.53-0.68)
Family history						
Family history	1,193	1.0 (Reference)	0.99 (0.83-1.19)	0.92 (0.78-1.08)	0.75 (0.64-0.89)	0.75 (0.62-0.91)
No family history	5,124	0.57 (0.50-0.65)	0.57 (0.50-0.65)	0.54 (0.48-0.62)	0.56 (0.49-0.64)	0.51 (0.44-0.58)

NOTE: Multivariate models used age as the underlying time metric and were adjusted for race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander/American Indian), education level (<12 years or high school equivalent, 12 years or high school equivalent, post-high school vocational or technical training, some college, college graduate, postgraduate), smoking status (nonsmoker, former, current), family history of breast cancer (no, yes), menopausal hormone use (never, current, past), age at first birth (nulliparous, <20, 20-24, 25-29, ≥30 years), age at menarche (<13, 13-14, ≥15 years), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 years), parity (number of children: 0, 1-2, ≥3), and alcohol intake (g/d; quintiles adjusted for total energy intake).

However, our results are consistent with the California Teachers Study, which found an inverse relation of physical activity to ER− breast cancer in postmenopausal women, whereas the association with ER+ tumors was null (19). A U.S. case-control study also showed a statistically nonsignificant inverse relation between adult activity and ER− tumors compared with a suggested positive association with ER+ tumors, although the study population was primarily premenopausal (20). Conversely, physical activity was selectively associated with reduced risk of ER+ postmenopausal breast cancer in the Iowa Women's Health Study (21). Furthermore, the relation of physical activity to breast cancer was not significantly modified by ER subtype in five case-control studies (22-26).

Our results regarding joint ER/PR status correspond to a recent systematic review (5) reporting a stronger association with ER−/PR− than ER+/PR+ tumors. In addition, our observation of a suggestive reduction in ER−/PR− cancer risk with increasing physical activity is consistent with results from the California Teachers Study (19) and a Shanghai-based case-control study (24). Physical activity was not associated with ER+/PR+ tumors in our study, in agreement with two other large cohort studies (19, 27) and two case-control studies (20, 23). In contrast, two studies (21, 24) reported an inverse association between physical activity and ER+/PR+ cancers. Associations with the less common discordant ER+/PR− and ER−/PR+ subtypes revealed no consistent pattern in our study and past studies (20, 21, 23, 24, 27).

Our study suggests a potential role of physical activity in the prevention of ER− breast cancers. This is of considerable interest because women with ER− cancers tend to be younger (28), to have tumors that are large and advanced at diagnosis (29), and to experience reduced survival (30). Moreover, there is currently a paucity of knowledge regarding risk factors for ER− tumors (18, 31).

The suggestion of a stronger relation with ER− than ER+ tumors also indicates that physical activity may influence breast cancer risk independently of estrogens. Potential alternative mechanisms include decreased levels of circulating insulin and insulin-like growth factors, reduction of chronic inflammation, and modulation of the immune response (8).

However, because estrogen may actually mediate the development of ER− tumors through growth signals produced by adjacent ER+ cells following estrogen exposure (32), physical activity could relate to ER-tumors through estrogenic mechanisms. It remains unresolved whether ER+ and ER− tumors represent two phases of one unified disease process or two distinct pathologic entities (33), although heterogeneity in correlated risk factors (9-11) and unique genetic profiles (34) for each subtype support the latter hypothesis. Moreover, estrogen metabolites may influence breast cancer risk independently of the ER via DNA damage (35).

In accordance with other reports (19, 22, 26, 36-38), we found no significant heterogeneity in the relation of physical activity to invasive versus *in situ* breast cancers, although we did note only a weak association with *in situ* tumors, similar to the Collaborative Breast Cancer Study (39). In contrast, the Cancer Prevention Study II (40) reported an inverse relation for physical activity specific to localized tumors, whereas a Polish case-control study (26) observed a stronger relation with advanced tumors. Taken together, our results along with most, but not all, epidemiologic evidence suggest that physical activity operates at all stages of breast cancer pathogenesis.

Our observation that the association with physical activity does not vary by breast tumor histology is consistent with the only other report on this relation (26), suggesting that physical activity reduces risk of both ductal and lobular carcinomas.

We found a suggestively more pronounced inverse association with physical activity for heavy than lean women, contrasting somewhat with a recent review (5) showing a greater reduction in breast cancer risk with increasing physical activity among lean than heavy women.

We observed a lower breast cancer risk among active versus inactive women who had never used MHT compared with those with past or current MHT use, similar to results for active non-Hispanic White women with no recent MHT use in one previous investigation (25). However, other studies (19, 22, 37, 38, 40-46) have not observed effect modification of the physical activity-breast cancer relation by MHT use. One possible explanation is limited statistical power to examine effect modification by MHT use in those studies (19, 22, 37, 38, 40-46). A differential association by MHT use indicates that physical activity affects breast cancer risk at least partially through a reduction in circulating sex hormones (7). Conceivably, exogenous estrogens taken by postmenopausal women may render such individuals less sensitive to any physical activity effect if physical activity most effectively reduces breast cancer risk at low estrogen levels.

In our study, physical activity was particularly associated with reduced breast cancer risk in women with a positive family history of breast cancer. This is not consistent with previous observations of either no effect modification or a stronger inverse relation for women without a family history (5). Apart from chance, one possible explanation for our finding is a greater potential for residual confounding by MHT use or other reproductive variables among women with a family history of breast cancer compared with those without a family history. If true, our finding suggests that women with hereditary risk require a lower ''dose'' of physical activity to alter their risk profile. This would have implications for targeting a subgroup of individuals who would most benefit from a physical activity intervention.

A major strength of our study is the large number of breast cancer cases. With nearly twice the number of incident cancers than any previous prospective study of the physical activity-breast cancer relation (3), we had ample statistical power to investigate the association by tumor characteristics and by select breast cancer risk factors. However, it is possible that some of our subgroup results emerged by chance due to multiple comparisons. The prospective nature of our data collection helped avoid recall bias, and comprehensive data on lifestyle covariates allowed extensive control for potential confounding. Because physical activity may serve as a proxy for an overall healthy lifestyle, we adjusted for numerous potentially confounding factors.

A limitation of our study includes the physical activity assessment, which queried participants' activity

by self-report and did not measure all physical activity parameters. However, bias related to misreporting of true activity levels would likely be nondifferential and would tend to underestimate the association between physical activity and breast cancer risk. In addition, our physical activity classification predicts cardiovascular mortality (47); this biologically plausible relation is consistent with the accumulated evidence and shows construct validity in the discriminatory ability of our five activity categories. An additional, although not necessarily critical, limitation is that the generalizability of our results may be limited because of the relatively low response proportion to our initial postal questionnaire.

Due to the very limited number of premenopausal participants in our cohort, we restricted the study population to postmenopausal women. Although this slightly reduced our cohort size, evidence of a stronger relation between physical activity and postmenopausal breast cancer (5), divergent associations between lifestyle factors such as BMI and risk of premenopausal versus postmenopausal breast cancer (2, 4, 5), and distinct incidence profiles for ER+ and ER− tumors by menopausal status (28) warrants our approach of excluding premenopausal women.

In summary, physical activity was associated with a modest reduction in the risk of postmenopausal breast cancer, particularly ER− tumors. In addition, the physical activity-breast cancer relation was modified by family history of breast cancer and by the estrogen-related factors MHT use and BMI. Our results suggest the potential for prevention of the comparatively aggressive ER− breast cancer subtype, and observation of a more pronounced inverse association between physical activity and breast cancer risk among certain subgroups of women may have practical implications for targeting an at-risk population. Future studies with large cohorts will be imperative for replication of our subgroup findings, and experimental studies and controlled trials will be required to elucidate the potential biological mechanisms underlying the association between physical activity and breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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