Recreational Physical Activity and Risk of Postmenopausal Breast Cancer Based on Hormone Receptor Status

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Background: Physical activity is a potentially modifiable breast cancer risk factor. There is considerable recent evidence to suggest that risk factors for breast cancer differ based on its subtype, particularly estrogen receptor (ER)/progesterone receptor (PR) status, but this has been less well studied for physical activity. The objective of this study was to examine the association of physical activity with breast cancer incidence based on ER/PR status of the tumor.

Methods: The Iowa Women's Health Study is a prospective cohort study of 41 836 postmenopausal women. Recreational physical activity was self-reported on the baseline questionnaire, and 3 levels (high, medium, and low) were defined. Breast cancer incidence and ER/PR status, through 18 years of follow-up, were ascertained by linkage with the Iowa Surveillance, Epidemiology, and End Results Cancer Registry. Cox proportional hazards models were used to estimate multivariate relative risks (RRs) and 95% confidence intervals (CIs) of breast cancer, adjusting for other breast cancer risk factors.

Results: During 554 819 person-years of follow-up, 2548 incident cases of breast cancer were observed. Compared with low physical activity, high physical activity levels were inversely associated with risk of breast cancer (RR, 0.86; 95% CI, 0.78-0.96), and there were inverse associations for ER-positive (ER^+)/PR-positive (RR, 0.87; 95% CI, 0.75-1.00), ER^+/PR-negative (PR^-) (RR, 0.67; 95% CI, 0.47-0.96), and ER-negative/PR^- (RR, 0.80; 95% CI, 0.56-1.14) tumors. Further adjustment for body mass index attenuated the overall association with breast cancer (RR, 0.91; 95% CI, 0.82-1.01) and for ER^+/PR-positive tumors (RR, 0.94; 95% CI, 0.81-1.08), while there was no change for ER^+/PR^- tumors (RR, 0.66; 95% CI, 0.46-0.94).

Conclusions: Higher recreational physical activity might reduce the risk of postmenopausal breast cancer overall. Risk reduction varies by ER/PR status of the tumor, being most marked for ER^+/PR^- tumors, which, in general, have been associated with a clinically more aggressive tumor phenotype. If confirmed in additional studies, these results would suggest that additional mechanisms, besides an effect on body mass, may account for observed protective effects of physical activity in reducing breast cancer.

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BREAST CANCER IS THE MOST common noncutaneous cancer and is the second leading cause of cancer-related death among women in the United States.[1,2] The incidence of breast cancer is increasing worldwide, and this seems to be partially related to an increase in some lifestyle risk factors for breast cancer, including obesity.[3-9]

Physical activity is a potentially modifiable breast cancer risk factor. Increased physical activity has been associated with a decreased risk of breast cancer among premenopausal and postmenopausal women.[10-25] However, a few studies have reported no benefit[26-31] or an increased risk.[32] It is suggested that breast cancer may be biologically heterogeneous and, therefore, risk factor associations may differ based on the tumor characteristics, including estrogen receptor (ER) and progesterone receptor (PR) status.[5,33-48] Recent studies have found that various well-established risk factors for breast cancer vary by the ER/PR profile of the tumor, including age,[34] menopausal status,[34,37] parity,[33,38-40] age at menarche,[38,41] age at first pregnancy,[34,37,39,40] hormonal use,[33,34,42-44] family history,[42,45] body mass index (BMI),[33,34,38,42,46] waist-hip ratio,[47] alcohol consumption,[35,42,48] dietary fat intake,[49] and folate level.[5,48] However, only 2 recent case-control studies[46,50] and 1 cohort study[16] have evaluated the association of physical activity with postmenopausal breast cancer incidence defined by joint ER/PR status, and the single cohort study was small (411 cases) and only reported results for ER-positive (ER^+)/PR-positive (PR^+) tumors.[16]

The Iowa Women's Health Study is a large prospective cohort of postmeno-

Table 1. Selected Demographic and Breast Cancer Risk Factors According to Level of Physical Activity at Study Baseline: Iowa Women's Health Study (1986)

Characteristic	Physical Activity Index*		
	Low (n = 17 222)	Medium (n = 10 030)	High (n = 9111)
Age, y†			
At baseline (1986)	61.5 ± 4.2	61.8 ± 4.2	61.8 ± 4.2
At menarche	12.9 ± 1.5	12.8 ± 1.4	12.8 ± 1.5
At menopause	47.4 ± 6.5	47.8 ± 6.3	47.9 ± 6.3
Body mass index†‡			
At the age of 18 y	21.7 ± 3.3	21.6 ± 3.0	21.5 ± 2.9
In 1986	27.7 ± 5.6	26.7 ± 4.7	26.1 ± 4.4
First-degree family history of breast cancer	12.2	11.7	12.4
>High school graduate	34.4	41.4	45.4
Nulliparous	9.0	9.0	9.2
Age at first live birth <20 y	22.0	18.5	17.2
Ever oral contraceptive use	18.7	18.5	18.8
Ever hormone therapy use	36.7	39.5	38.6
No alcohol intake	59.3	53.2	53.8
Ever a smoker	37.4	31.3	31.7

*Data are given as percentage of each group unless otherwise indicated.
†Data are given as mean ± SD.
‡Calculated as weight in kilograms divided by the square of height in meters.

pausal women. A nonsignificant inverse association of physical activity with breast cancer was previously reported after 10 years of follow-up (adjusted relative risk [RR], 0.97; 95% confidence interval [CI], 0.87-1.08).[31] We present the updated results of this previous study after an additional 8 years of follow-up, along with results stratified by ER/PR status of the tumor.

METHODS

STUDY POPULATION

The Iowa Women's Health Study is a prospective cohort study of 41 836 women aged 55 to 69 years initiated in 1986, and details about characteristics of the cohort have been described previously.[51,52] Briefly, a 16-page questionnaire was mailed to 99 826 randomly selected women and returned by 41 836 women (41.9% response rate), with follow-up questionnaires mailed in 1987, 1989, 1992, 1997, and 2002.

MEASUREMENT OF RISK FACTORS

Physical activity during "free time" was ascertained using 2 questions that assessed frequency ("rarely or never," "a few times a year," "a few times a month," "about once a week," "two to four times a week," or "more than four times a week") and type of physical activity in the form of moderate activity (such as bowling, golf, light sports, gardening, or taking long walks) and of vigorous activity (such as jogging, racket sports, swimming, aerobics, or strenuous sports). This level of moderate physical activity generally requires fewer than 6 metabolic equivalent (resting metabolic rate or metabolic equivalent of energy expenditure) hours per week, and vigorous physical activity generally requires 6 or more metabolic equivalent hours per week.[53]

Based on these questions, 3 levels of physical activity were derived. *High physical activity* was defined as participation in vigorous activity 2 or more times per week or moderate activity more than 4 times per week. *Medium physical activity* was defined as participation in vigorous activity once per week or moderate activity 1 to 4 times per week. *Low physical activity* composed the rest of the cohort. This physical activity index has been indirectly validated in the cohort by the observation that BMI and mean energy intake vary by level of physical activity, and higher physical activity is inversely associated with overall and cardiovascular disease–related mortality.[54,55]

COHORT FOLLOW-UP

Incident cases of breast cancer, including ER/PR status, were identified through 2003 using the Iowa Cancer Registry, a member of the National Cancer Institute's Surveillance, Epidemiology, and End Results program.[2] Each year, registry cases and cohort members were matched against registry files on name, maiden name, ZIP code, birth date, and social security number. Deaths were identified through annual linkage to Iowa death certificates, supplemented by linkage to the National Death Index.

EXCLUSION

Women who at baseline were premenopausal (n=569), had cancer other than skin cancer (n=3830), had undergone a total or partial mastectomy (n=1884), or did not have data about physical activity (n=742) were excluded from the analysis, leaving 36 363 participants for this analysis (exclusions are not mutually exclusive).

STATISTICAL ANALYSIS

Follow-up for incident events was calculated as the time from completion of the baseline questionnaire until the date of breast cancer diagnosis, date of move from Iowa, or date of death. Cox proportional hazards regression analysis was used to estimate RRs and 95% CIs of the association of physical activity with breast cancer risk based on ER/PR tumor subtype, controlling for potential confounding factors as outlined in **Table 1**. Because one of the mechanisms by which physical activity is postulated to decrease breast cancer risk is through decreasing adi-

posity,[56-58] we modeled the association with and without controlling for obesity (BMI and BMI at the age of 18 years). Incidence was modeled as a function of age, because age is a better predictor of breast cancer risk in this cohort than length of follow-up.[59] Tests for trend were calculated using an ordinal variable for level of physical activity, and including it in the Cox proportional hazards model as a linear variable. In the receptor-specific analyses, events not of that specific cancer type were considered censored observations. Population-attributable risk estimates were calculated based on the coefficients generated by the Cox proportional hazards models and the distribution of physical activity in the cohort.[60] Confidence intervals were generated using the bootstrap resampling method.[61] All statistical tests were 2-sided, and all analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC) and Splus software (Insightful, Inc, Seattle, Wash).

RESULTS

There were 36 363 postmenopausal women aged 55 to 69 years at baseline in the analytic data set, and 99.2% were white. Compared with women with a low physical activity index, women with a high physical activity index had a lower BMI. They were also slightly more likely to be higher educated, to have a later age at first live birth, to consume alcohol, and to not smoke (Table 1). All other risk factors showed negligible differences with level of physical activity.

During 554 819 person-years of follow-up, 2548 incident cases of breast cancer were observed in the postmenopausal cohort. The mean age at diagnosis of breast cancer was 71.4 years. Estrogen receptor/PR status was available for 73.0% of the cases and of those with receptor status available, most were ER^+/PR^+ (71.1%), followed by ER^+/PR negative (PR^-) (13.5%), ER negative (ER^-)/PR^- (13.1%), and ER^-/PR^+ (2.3%). The availability of ER or PR was related to stage (highest for local and regional cases and lowest for in situ), but, of those cases with ER or PR, the percentage positive did not vary strongly with stage (eg, 73.1% of in situ, 85.9% of local, 82.7% of regional, and 75.0% of distant cases were ER^+).

Compared with women with low physical activity levels, women with high physical activity levels had a 14% decreased risk of breast cancer after adjusting for major breast cancer risk factors, with the exception of the BMI variables (**Table 2**). This inverse association was strongest for ER^+ and PR^- tumors, while there were weaker inverse associations for ER^- and PR^+ tumors. Cross classification by receptor status showed an inverse relationship of physical activity with each breast cancer subtype except ER^-/PR^+, which showed a statistically nonsignificant positive association (P=.56); the fewer cases in this subtype limits interpretation of this result. The strongest association was seen for ER^+/PR^- tumors.

Next, we further adjusted the RRs for BMI at study baseline (1986) and for BMI at the age of 18 years (Table 2). The inverse association of physical activity attenuated for breast cancer overall and for ER^+, PR^+, and ER^+/PR^+ tumors. In contrast, the results changed little for ER^-, PR^-, and ER^+/PR^- tumors. Further adjustment for waist-hip ratio did not alter these results (data not shown).

There were no significant interactions between previously reported common effect modifiers for breast cancer[48,62] (BMI [P=.10], waist-hip ratio [P=.43], family history of breast cancer [P=.87], and smoking [P=.37]) and physical activity on incidence of breast cancer, either overall or by ER/PR status (results not shown).

Population-attributable risks (given in percentages) were calculated to estimate the potential public health significance if physical activity levels were increased to the high level of the physical activity index. Multivariate-adjusted population-attributable risks (not including BMI and BMI at the age of 18 years) were 10.9 (95% CI, 3.9-18.0) for all breast cancer, 7.9 (95% CI, 0-17.0) for ER^+/PR^+ tumors, 28.4 (95% CI, 7.4-49.4) for ER^+/PR^- tumors, and 21.9 (95% CI, 0-42.7) for ER^-/PR^- tumors; the latter estimate included no effect because the RR estimate for ER^-/PR^- tumors was not statistically significant.

COMMENT

This is the first large prospective cohort study, to our knowledge, to comprehensively report the association of physical activity on incidence of breast cancer by ER/PR status among postmenopausal women. We found that higher recreational physical activity was associated with about 14% decreased risk of breast cancer. The inverse association seemed to vary by ER/PR status and was most marked among ER^+/PR^- tumors (33% lower risk). Adjustment for BMI attenuated associations for all breast cancer and for ER^+/PR^+ tumors, but not for ER^+/PR^- tumors.

The study findings of a 14% lower risk of breast cancer among the most physically active women is within the range reported by most case-control and cohort studies[10-25] involving postmenopausal women. A recent report[25] from the Women's Health Initiative Cohort Study involving 74 171 women reported a 14% lower risk of breast cancer for women engaged in regular strenuous physical activity at the age of 35 years (95% CI, 0.78-0.95) and an 8% lower risk for women engaged in regular physical activity at the age of 50 years (95% CI, 0.83-1.01). Similar results were found for ER^+ tumors, but results for PR and the joint classification of ER/PR were not conducted. Lee et al[16] also reported an inverse association of physical activity with breast cancer among postmenopausal women (RR, 0.67; 95% CI, 0.44-1.02) in the Women's Health Study cohort, and results were similar when restricted to ER^+/PR^+ tumors (RR, 0.76; 95% CI, 0.43-1.34); no data were reported for other subtypes because of the small sample size.

Two case-control studies[46,50] have provided results for joint ER/PR status among postmenopausal women. Similar to our results, Enger et al[46] found that higher physical activity had a stronger effect in reducing ER^+/PR^- tumors (odds ratio, 0.43; 95% CI, 0.19-0.98) than ER^+/PR^+ tumors (odds ratio, 0.69; 95% CI, 0.42-1.13). Another case-control study[63] found the effect of vigorous physical activity to be slightly stronger among ER^+ tumors (odds ratio, 0.79; 95% CI, 0.68-0.93) than ER^- tumors (odds ratio, 0.86; 95% CI, 0.70-1.05), but did not further cross classify the tumors. Two other case-control studies found little evidence for causative heterogeneity for the asso-

Table 2. Association of Physical Activity With Breast Cancer Incidence: Iowa Women's Health Study (1986-2003)

Characteristic*	Physical Activity Index†			*P* Value for Trend
	Low	Medium	High†	
Person-years	259 247	154 392	141 180	NA
All breast cancer cases				
No. of cases	1216	750	582	NA
RR (95% CI)				
Adjustment 1	1.00	1.01 (0.91-1.11)	0.86 (0.78-0.96)	.01
Adjustment 2	1.00	1.04 (0.94-1.14)	0.91 (0.82-1.01)	.13
ER^+ cases				
No. of cases	808	468	367	NA
RR (95% CI)				
Adjustment 1	1.00	0.95 (0.84-1.07)	0.82 (0.72-0.94)	.004
Adjustment 2	1.00	0.98 (0.87-1.11)	0.87 (0.77-1.00)	.06
ER^- cases				
No. of cases	129	100	69	NA
RR (95% CI)				
Adjustment 1	1.00	1.20 (0.91-1.59)	0.90 (0.66-1.23)	.69
Adjustment 2	1.00	1.21 (0.92-1.60)	0.92 (0.67-1.25)	.78
PR^+ cases				
No. of cases	668	376	322	NA
RR (95% CI)				
Adjustment 1	1.00	0.92 (0.81-1.05)	0.88 (0.77-1.01)	.07
Adjustment 2	1.00	0.96 (0.84-1.10)	0.95 (0.82-1.09)	.45
PR^- cases				
No. of cases	229	168	100	NA
RR (95% CI)				
Adjustment 1	1.00	1.17 (0.95-1.45)	0.74 (0.57-0.95)	.06
Adjustment 2	1.00	1.16 (0.94-1.43)	0.73 (0.65-0.94)	.04
ER^+/PR^+ cases				
No. of cases	648	366	309	NA
RR (95% CI)				
Adjustment 1	1.00	0.92 (0.81-1.06)	0.87 (0.75-1.00)	.05
Adjustment 2	1.00	0.96 (0.84-1.11)	0.94 (0.81-1.08)	.37
ER^+/PR^- cases				
No. of cases	123	81	48	NA
RR (95% CI)				
Adjustment 1	1.00	1.08 (0.80-1.46)	0.67 (0.47-0.96)	.06
Adjustment 2	1.00	1.06 (0.78-1.43)	0.66 (0.46-0.94)	.04
ER^-/PR^+ cases				
No. of cases	19	10	13	NA
RR (95% CI)				
Adjustment 1	1.00	0.88 (0.39-1.99)	1.29 (0.61-2.72)	.56
Adjustment 2	1.00	0.91 (0.40-2.06)	1.42 (0.67-3.01)	.41
ER^-/PR^- cases				
No. of cases	106	86	52	NA
RR (95% CI)				
Adjustment 1	1.00	1.26 (0.93-1.70)	0.80 (0.56-1.14)	.40
Adjustment 2	1.00	1.26 (0.93-1.70)	0.80 (0.56-1.15)	.40
Unknown ER/PR status				
No. of cases	320	207	160	NA
RR (95% CI)				
Adjustment 1	1.00	1.07 (0.89-1.28)	0.91 (0.75-1.11)	.46
Adjustment 2	1.00	1.10 (0.92-1.32)	0.96 (0.79-1.18)	.87

Abbreviations: CI, confidence interval; ER^+, estrogen receptor positive; ER^-, ER negative; NA, data not applicable; PR^+, progesterone receptor positive; PR^-, PR negative; RR, relative risk.

*Adjustment 1 included adjustment for age, educational level, family history of breast cancer, age at menarche, number of live births, age at first live birth, oral contraceptive use, age at menopause, use of hormone therapy, alcohol use, and smoking; and adjustment 2, all adjustments in adjustment 1 plus adjustment for body mass index at baseline (1986) and body mass index at the age of 18 years.

†High is defined as vigorous activity 2 times per week or more or moderate activity more than 4 times per week; medium, vigorous activity once per week or moderate activity 1 to 4 times per week; and low, less than moderate activity.

ciation of physical activity with ER/PR subtypes among premenopausal[50,64] or postmenopausal[64] women.

Our ER/PR subtype results for physical activity parallel those for reductions in fat intake seen in the Women's Health Initiative, a randomized trial of 48 835 postmenopausal women. Women who reduced intake of total fat to 20% of energy had a markedly lower risk of ER^+/PR^- tumors (RR, 0.64; 95% CI, 0.49-0.84), but not $ER^+/$

PR^+ tumors (RR, 0.97; 95% CI, 0.86-1.10).[36] The ER^+/PR^- tumors seem to represent a more clinically aggressive phenotype.[65] For example, ER^+/PR^- tumors are often larger,[65] have a higher grade,[65] have more resistance to selective ER modulators,[66-68] and have a worse prognosis,[65,68-70] compared with ER^+/PR^+ tumors.

Physical activity decreases the endogenous production of estrogen by reducing adipose tissue, the major source of estrogens in postmenopausal women.[56-58] Lowering estrogen levels could lead to decreased ER^+/PR^+ tumors, the opposite of which is seen in obesity, in which increased circulating estrogens are associated with increased ER^+/PR^+ tumors.[33,34,38,41,42,46] Consistent with this mechanism, the association of physical activity with ER^+/PR^+ tumors attenuated after adjustment for BMI. In contrast, there was no change in the association for ER^+/PR^- tumors after adjustment for BMI, suggesting that additional mechanisms are likely to be important for this subtype. Higher levels of certain growth factors, particularly epidermal growth factor receptor or human growth factor receptor 2, have been associated with ER^+/PR^- tumors.[70] Physical activity seems to impact growth factor levels,[57,71,72] and this might in part explain the ER^+/PR^- results.

This study had a few limitations. First, physical activity was measured as a single self-reported assessment at baseline (1986), with no update during follow-up. Also, it did not include detailed aspects of physical activity, such as lifetime activity, seasonal patterns, or occupational activity, and we were not able to calculate metabolic equivalents. However, previous reports[54,55] from the Iowa Women's Health Study cohort have indicated that this physical activity index is sensitive enough to identify major disease trends. Second, information about ER/PR status of breast cancer was obtained through multiple pathological laboratories, rather than a single reference laboratory. However, the ER/PR distribution in our study was similar to that reported by other studies.[34,73] Finally, most of the population in the study was white. However, physical activity has been shown to have a beneficial effect on breast cancer among other races.[63]

In summary, higher physical activity was associated with about a 14% decreased risk of postmenopausal breast cancer. The inverse association was most marked for ER^+ tumors, particularly ER^+/PR^- tumors; the latter, in general, have been associated with a more aggressive phenotype. The results also suggest that additional mechanisms, besides an effect on body mass, may account for observed effects of physical activity for this subtype. Further studies are needed to confirm these novel findings, and to evaluate similar relationships among premenopausal women. If found to be causally related to breast cancer, physical activity would have a substantial public health effect on the prevention of this disease, along with its other positive health benefits.[74]

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