Short Communication

Cancer Epidemiology, Biomarkers & Prevention

Recreational Physical Activity and Leisure-Time Sitting in Relation to Postmenopausal Breast Cancer Risk

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Abstract

Epidemiologic evidence supports an inverse association between physical activity and postmenopausal breast cancer. Whether associations exist for moderate activities, such as walking, and whether associations differ by estrogen receptor (ER) status, body mass index (BMI, kg/m^2), adult weight gain, or use of postmenopausal hormones (PMH) is unclear. The relation between time spent sitting and breast cancer also is unclear. Among 73,615 postmenopausal women in the American Cancer Society Cancer Prevention Study II Nutrition Cohort, 4,760 women were diagnosed with breast cancer between 1992 and 2009. Extended Cox regression was used to estimate multivariable-adjusted relative risks (RR) of breast cancer in relation to total recreational physical activity, walking, and leisure-time sitting. Differences in associations by ER status, BMI, weight gain, and PMH use were also evaluated. The most active women (those reporting >42 MET-hours/week physical activity) experienced 25% lower risk of breast cancer than the least active [0–<7 MET-hours/week; 95% confidence interval (CI), 0.63–0.89; $P_{trend} = 0.01$]. Forty-seven percent of women reported walking as their only recreational activity; among these women, a 14% lower risk was observed for ≥7 hours/week relative to ≤3 hours/week of walking (95% CI, 0.75–0.98). Associations did not differ by ER status, BMI, weight gain, or PMH use. Sitting time was not associated with risk. These results support an inverse association between physical activity and postmenopausal breast cancer that does not differ by ER status, BMI, weight gain, or PMH use. The finding of a lower risk associated with ≥7 hours/week of walking may be of public health interest. *Cancer Epidemiol Biomarkers Prev; 22(10); 1906–12. ©2013 AACR.*

Introduction

In 2007, the World Cancer Research Fund/American Institute for Cancer Research concluded that sufficient epidemiologic evidence exists for a probable inverse association between physical activity and postmenopausal breast cancer (1). More than 70 observational studies support an approximate 25% lower risk of breast cancer among physically active, relative to inactive, women (2). However, questions about the association remain unanswered. Although the evidence supports an association for regular vigorous physical activity, it is unclear whether activities of moderate intensity, such as walking, impart a benefit in the absence of vigorous exercise. In addition, whether associations differ by molecular features, such as hormone receptor status, or by individual factors such as weight status and use of postmenopausal hormones (PMH) is unclear. PMH use is known to modify associations between excess weight and breast cancer where a positive association is observed only in nonusers (3). Furthermore, while prolonged periods of sitting have been associated, independent of physical activity, with premature mortality, cardiovascular disease, type II diabetes mellitus, as well as some cancers (4), the relation between sitting time and postmenopausal breast cancer risk is not well understood (5, 6).

It has been noted that large prospective studies are needed to clarify whether associations between physical activity and breast cancer differ by hormone receptor status, body mass index (BMI, kg/m^2), weight gain, or PMH use (7). An inverse association between recreational physical activity and incident postmenopausal breast cancer in the American Cancer Society Cancer Prevention Study II (CPS-II) Nutrition Cohort was previously reported (8). However, that study was not sufficiently powered to examine subgroup associations, nor was time spent sitting evaluated. With 12 years of additional follow-up time, we examined total recreational physical activity, walking, and leisure-time sitting in relation to postmenopausal breast cancer incidence. Associations also were assessed by estrogen receptor (ER) status, BMI, adult weight gain, and PMH use.

Materials and Methods

Study population

Subjects were drawn from the 97,785 women participants in the CPS-II Nutrition Cohort, a prospective study

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doi: 10.1158/1055-9965.EPI-13-0407

of cancer incidence established by the American Cancer Society in 1992 (9). The Nutrition Cohort is a subgroup of the CPS-II baseline mortality cohort (10). Participants of ages 50 to 74 years were enrolled in the study in 1992–93 when they completed a 10-page, self-administered questionnaire on demographic, reproductive, medical, environmental, and behavioral factors. Beginning in 1997, follow-up questionnaires have been sent to participants every 2 years to update exposure information and to ascertain newly diagnosed cancers. Response rates among living cohort members are 88% or more.

Excluded from the analysis were 3,111 women lost to follow-up (i.e., alive at first follow-up but did not return any follow-up questionnaire), who reported prevalent cancer (except non-melanoma skin cancer) at enrollment ($N = 12{,}059$), were pre/peri-menopausal ($N = 4{,}712$), or missing information on recreational physical activity, sitting time, or BMI ($N = 4{,}222$). Women who reported breast cancer on their first follow-up questionnaire, that was never verified, were also excluded ($N = 66$). The final cohort for analysis consisted of 73,615 postmenopausal women (i.e., whose periods had stopped permanently before enrollment, naturally or for surgical/medical reasons) with a mean age of 62.7 years and median follow-up time of 14.2 years between enrollment and June 30, 2009, which marked the end of follow-up for this analysis.

Case ascertainment

Of the 4,760 incident breast cancer cases [International Classification of Diseases for Oncology (ICD-O) topography code C50] diagnosed among the cohort during follow-up, 4,662 cases were initially identified by self-report and subsequently verified by medical records or linkage with state cancer registries. Sensitivity of self-reported cancer in this cohort has been estimated to be 93% (11). An additional 98 incident cases were identified through automated linkage with the National Death Index (12), of which 78 were subsequently verified via linkage to state registries. Of the 69% of cases with available ER status (+/−), 84% ($N = 2806$) were ER^+ and 15% ($N = 498$) were ER^-.

Assessment of physical activity and time spent sitting

Information on weekly recreational activities was collected at enrollment as described in detail elsewhere (8). The average number of hours/week spent in each of the following activities was assessed: walking, jogging/running, lap swimming, tennis/racquetball, bicycling/stationary bike, aerobics/calisthenics, and dancing. A summary estimate of total hours/week of the metabolic equivalent (MET), which is an estimate of the ratio of the energy expenditure during a specific activity to the resting metabolic rate, was calculated for each individual (13). Women who reported no activity were categorized as "none," and the remaining (active) women were categorized according to quintiles of MET-hours/week (>0–7.0, >7.0–17.5, >17.5–31.5, >31.5–42.0, and >42.0). Hours/week of walking was categorized consistent with questionnaire response categories (none, ≤3, 4–6, and ≥7). Because declining health or chronic conditions associated with aging or low estrogen (e.g., osteoporosis) may prevent some women from engaging in even light recreational physical activity, women reporting the lowest level of activity, as opposed to "none," comprised the referent group for these comparisons.

Leisure-time sitting (time spent watching TV, reading, etc.) was categorized as 0–<3 (referent), 3–5, or ≥6 h/d, based on questionnaire response categories.

Physical activity and time spent sitting were requeried and updated in 1999, 2001, and 2005.

Statistical analysis

Follow-up time for each participant was calculated as person-years from the date of completion of the enrollment questionnaire to the date of: (i) diagnosis of breast cancer; (ii) death; (iii) the last cancer-free questionnaire when unverifiable breast cancer was self-reported on a subsequent questionnaire; (iv) the last completed questionnaire if no subsequent follow-up questionnaire was returned or if the follow-up questionnaire was missing information on physical activity; (v) June 30, 2009. Extended Cox regression was used to estimate age-adjusted and multivariable-adjusted hazard rate ratios for approximation of relative risks (RR) with 95% confidence intervals (CI; ref. 14). Multivariable-adjusted models included race, education, BMI, adult weight change (from age of 18 years to age at enrollment), alcohol intake, smoking status, age at menopause, number of live births/age at first live birth, personal history of breast cysts, hysterectomy or oophorectomy, family history of breast cancer, mammography, and PMH use (never, current, or former). We evaluated the influence of type and duration of PMH on the associations of interest, but found that adjustment for current hormonal status controlled for confounding equally as well as a variable also defining type and duration of use. PMH use and mammography were updated in 1997, 1999, 2001, 2003, and 2005. All models were stratified on age at enrollment.

P values for statistical significance of heterogeneity of associations between ER^+ and ER^- breast cancer were derived from the Cochran *Q* test statistic, generated from meta-analysis procedures (15). Effect modification by BMI (<25 or ≥25 kg/m^2), adult weight gain (≤35 or >35 lbs.), and PMH use (never/former or current) was assessed in stratified analyses; *P* values for statistical significance of interaction were generated by likelihood ratio tests comparing models of cross-product terms with models of independent main effects. Linear trend of RR in relation to MET-hours/week was tested with a variable defining the median value of each category of MET-hours/week, and the *P* value was derived from the Wald χ^2 statistic. All tests for statistical significance were two-sided.

Results

Approximately, 9.2% ($n = 6{,}747$) of women reported no recreational physical activity at baseline (Table 1). The

Table 1. Baseline characteristics of CPS-II Nutrition Cohort women according to level of recreational physical activity measured as MET expenditure per week

	MET-h/wk					
Characteristic	**None (n = 6,747)**	**>0–7.0 (n = 25,084)**	**>7–17.5 (n = 23,743)**	**>17.5–31.5 (n = 13,649)**	**>31.5–42.0 (n = 2,391)**	**>42.0 (n = 2,001)**
Median MET-h/wk	0.0	3.5	13.5	24.5	35.5	52.5
Average age in 1992, y	62.6	62.7	62.7	62.9	62.4	62.6
			Age-adjusted percentage[a]			
Race						
White	96.9	97.3	97.4	97.4	97.5	97.0
Non-White	3.1	2.7	2.6	2.6	2.5	3.0
Education						
High school graduate or less	47.3	39.3	34.9	34.5	28.6	26.1
Some college or trade	29.3	31.6	31.6	31.6	34.4	31.5
College graduate	22.7	28.5	32.9	33.2	36.6	41.8
Missing	0.7	0.7	0.7	0.7	0.5	0.7
Sitting h/d						
<3	40.5	46.4	47.7	49.0	51.4	52.2
3–5	43.5	43.9	43.4	41.3	39.7	37.1
6+	16.0	9.8	8.9	9.6	8.9	10.6
BMI, kg/m^2						
<18.5	2.3	1.7	1.8	2.1	2.2	3.7
18.5–<25.0	39.7	47.2	52.4	56.7	62.6	64.3
25.0–<30.0	32.6	33.3	31.9	29.9	27.3	23.9
≥30.0	25.4	17.8	13.9	11.3	7.9	8.0
Adult weight change						
>5 lb. loss	6.1	5.6	6.4	7.5	8.3	11.6
≤5 lb. gain or loss	6.4	7.9	9.2	11.2	13.5	15.1
>5 to 15 lb. gain	11.9	14.5	17.1	18.7	23.3	21.0
>15 to 25 lb. gain	14.1	17.2	18.6	19.0	18.5	17.3
>25 to 35 lb. gain	14.6	16.3	16.0	15.8	14.7	13.2
>35 lb. gain	45.7	37.5	31.6	26.7	21.0	20.6
Alcohol intake						
Nondrinker	54.8	48.9	44.1	42.4	35.1	35.0
<1 drink/d	30.2	35.8	40.1	39.9	43.7	42.4
1+ drink/d	10.9	11.1	12.3	13.8	17.5	17.8
Missing	4.1	4.2	3.4	3.9	3.7	4.9
Smoking status						
Nonsmoker	50.5	57.2	55.2	53.3	49.7	47.8
Current smoker	13.8	8.8	7.0	7.8	7.5	8.5
Former smoker	34.3	32.7	36.6	37.6	41.8	41.8
Smoker-status unknown	0.4	0.3	0.3	0.4	0.3	0.8
Missing	1.0	0.9	0.9	0.9	0.7	1.1
Age at menopause, y						
<45	26.7	24.2	23.7	24.2	23.5	24.3
45–54	63.6	66.0	65.8	65.3	66.0	63.9
55+	8.7	9.0	9.9	9.9	10.0	10.9
Missing	0.9	0.7	0.6	0.6	0.5	0.8
Number live births by age at first live birth						
No live births	7.9	7.6	7.3	7.5	6.5	7.4
<24, 1–2 live births	16.6	16.0	15.2	16.0	15.5	15.1
25–29, 1–2 live births	11.5	11.5	12.1	11.6	11.8	13.2

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Table 1. Baseline characteristics of CPS-II Nutrition Cohort women according to level of recreational physical activity measured as MET expenditure per week (Cont'd)

	MET-h/wk					
Characteristic	None (n = 6,747)	>0–7.0 (n = 25,084)	>7–17.5 (n = 23,743)	>17.5–31.5 (n = 13,649)	>31.5–42.0 (n = 2,391)	>42.0 (n = 2,001)
30+, 1–2 live births	6.1	5.4	5.3	5.4	4.5	4.8
<20, 3+ live births	8.6	7.1	6.6	6.7	5.6	5.1
20–24, 3+ live births	30.8	32.6	33.6	33.0	35.1	33.1
25+, 3+ live births	15.7	17.3	17.6	17.3	18.4	18.4
Missing	2.8	2.4	2.2	2.5	2.6	2.9
PMH use						
Never	44.7	41.8	40.2	41.0	39.5	39.9
Current	23.8	27.6	29.0	28.4	28.5	28.8
Former	18.8	17.8	17.5	17.7	17.5	18.0
Missing	12.7	12.8	13.4	12.8	14.6	13.3
History of breast cysts						
No	72.9	71.1	71.2	72.1	70.1	72.7
Yes	27.1	28.9	28.8	27.9	29.9	27.3
Organs removed						
None or 1 ovary only	59.3	60.2	60.9	60.7	60.8	59.8
Uterus/1 or unknown ovaries	17.7	18.1	17.5	17.5	18.2	17.4
Both ovaries	20.4	19.9	20.0	20.1	19.4	20.7
Missing	2.5	1.9	1.5	1.7	1.6	2.1
Family history of breast cancer						
No	86.6	86.1	86.4	86.2	86.3	85.8
Yes	13.4	13.9	13.6	13.8	13.7	14.2
Mammography						
Not within the last year	42.1	34.5	31.9	32.1	29.9	28.5
Within the last year	56.7	64.7	67.3	67.1	69.3	70.9
Missing	1.2	0.8	0.8	0.8	0.8	0.7

[a]Adjusted to the age distribution of the Nutrition Cohort women.

median MET expenditure among active women was 9.5 MET-hours/week, which is equivalent to 3.5 hours/week moderately paced walking. Physically active women, regardless of the amount, engaged primarily in activities judged to be of moderate intensity (walking, cycling, aerobics, and dancing) rather than vigorous-intensity activities (jogging/running, swimming, tennis/racquetball); 47% of women reported walking as their only recreational activity. Physically active women tended to be leaner, more likely to maintain or lose weight during adulthood, more likely to drink alcohol, and less likely to currently smoke. They were also more likely to use PMH and to have had a mammogram in the past year. Sitting time was not correlated with recreational physical activity (Pearson $r = -0.05$).

Recreational physical activity was inversely associated with breast cancer incidence ($P_{trend} = 0.01$, active women only; Table 2). The most active women (those reporting >42.0 MET-hours/week) had a 25% lower risk of breast cancer relative to women in the least active category (>0–7.0 MET-hours/week; 95% CI, 0.63–0.89). Walking was inversely associated with breast cancer risk. Among women who reported walking as their only activity, those walking ≥7 hours/week had a 14% lower breast cancer risk relative to women walking ≤3 hours/week (95% CI, 0.75–0.98). No statistically significant heterogeneity of associations was observed by ER status (MET hours/week, $P = 0.70$; walking, $P = 0.99$; sitting time, $P = 0.08$), nor was there any evidence of interaction between exposures and BMI (MET hours/week, $P = 0.97$; walking, $P = 0.86$; sitting time, $P = 0.25$), adult weight gain (MET hours/week, $P = 0.82$; walking, $P = 0.56$; sitting time, $P = 0.44$) or PMH use (MET hours/week, $P = 0.97$; walking, $P = 0.99$; sitting time, $P = 0.06$).

A modest positive association between time spent sitting and breast cancer was observed in age-adjusted models. However, when adjusted for other factors including physical activity, the RR was attenuated and no longer statistically significant (Table 2).

Discussion

In this large prospective study of postmenopausal women, an inverse association was found between

Table 2. Relative risk of breast cancer according to measures of recreational physical activity and leisure-time sitting among women of the CPS-II Nutrition Cohort, 1992–2007

	RR according to exposure updated in 1999, 2001, and 2005			
	Cases/person-years	Rate[a]	RR (95% CI)[b]	RR (95% CI)[c]
MET-h/wk total recreational physical activity				
None	370/77,316	478	0.91 (0.81–1.02)	0.91 (0.81–1.02)
>0–7.0	1,706/317,697	533	1.00	1.00
>7–17.5	1,428/274,564	519	0.97 (0.90–1.04)	0.97 (0.90–1.04)
>17.5–31.5	875/164,808	522	0.99 (0.91–1.07)	0.99 (0.92–1.08)
>31.5–42.0	238/46,955	499	0.93 (0.81–1.07)	0.94 (0.82–1.08)
>42.0	143/35,566	393	0.74 (0.62–0.88)	0.75 (0.63–0.89)
		$P_{trend} = 0.05$ (active women only; $P_{trend} = 0.01$)[c,f]		
Walking h/wk				
None	370/77,316	478	0.89 (0.79–0.99)	0.89 (0.79–1.00)
≤3 h/wk walking only	1,474/267,826	546	1.00	1.00
4–6 h/wk walking only	521/106,028	490	0.89 (0.80–0.98)	0.91 (0.82–1.01)
≥7 h/wk walking only	260/56,530	440	0.82 (0.72–0.94)	0.86 (0.75–0.98)
≤3 h/wk walking plus[d]	1,147/215,229	530	0.97 (0.90–1.05)	0.95 (0.88–1.03)
4–6 h/wk walking plus[d]	513/93,770	541	0.99 (0.90–1.10)	1.00 (0.90–1.10)
≥7 h/wk walking plus[d]	240/52,664	447	0.82 (0.71–0.94)	0.83 (0.73–0.96)
Active nonwalkers[g]	111/20,446	545	1.01 (0.83–1.22)	0.97 (0.80–1.18)
Sitting h/d[e]				
<3	2,388/474,936	502	1.00	1.00
3–5	1,721/321,132	531	1.06 (1.00–1.13)	1.03 (0.97–1.10)
≥6	572/101,202	546	1.10 (1.01–1.21)	1.05 (0.96–1.16)
		$P_{trend} = 0.20$ (active women only; $P_{trend} = 0.26$)[c,e,f]		

[a]Standardized to the age-distribution of the Nutrition Cohort women.
[b]Age-adjusted.
[c]Adjusted for age, race, education, BMI (kg/m^2), weight change, alcohol use, smoking status, PMH use, number of live births, age at first live birth, age at menopause, family history of breast cancer, breast cysts, hysterectomy, oophorectomy, and mammogram within last year.
[d]Walking in addition to other recreational activities.
[e]Also adjusted for MET expenditure from total recreational activities.
[f]Women reporting no physical activity ("None") excluded from P_{trend} calculations.
[g]Women who engage in recreational activities other than walking.

physical activity and incident breast cancer. Walking on average at least 1 hour/day was modestly associated with lower risk, even in the absence of other recreational physical activities. Associations did not differ by ER status, BMI, adult weight gain, or PMH use. Time spent sitting was not associated with breast cancer incidence in this cohort.

Physical activity is consistently associated with lower risk of postmenopausal breast cancer (1). Our findings of a 25% lower RR associated with >42 MET-hours/week and a 14% lower RR associated with the equivalent of 1 hour/day walking are notably consistent with a review of more than 70 studies that reported a 28% reduction in risk and, in particular, a 15% reduction in risk attributable to less moderate physical activity, comparing the highest to lowest categories based on frequency, duration, and intensity (2). Current guidelines for adults recommend at least 150 minutes/week of moderate-intensity or 75 minutes/week of vigorous-intensity aerobic activity for overall health (16). Yet, less than half of U.S. adult women are active at these minimum levels (17), and thus an even smaller proportion of women likely achieve the higher levels thought necessary for breast cancer risk reduction. Given that more than 60% of women report some daily walking, promotion of leisure-time walking may be an effective strategy for increasing physical activity among postmenopausal women (18).

Among the few studies that examined differences in associations by ER status (19–21), no consistent patterns of variation have emerged. Our results, drawn from a large prospective cohort with more than 4,700 incident breast cancer outcomes, suggest that the association between

physical activity and lower risk does not vary by ER status, BMI, adult weight gain, or PMH use. A review of 22 studies that stratified results by BMI indicated only slightly stronger associations for physical activity in lean/normal weight (BMI <25 kg/m^2), as compared with overweight/obese (BMI ≥25 kg/m^2) women, and concluded that women of most body sizes likely benefited (2). However, a more recent review noted an approximate 27% lower risk for highest versus lowest levels of physical activity among women with a BMI of <22 kg/m^2 versus only 1% lower risk among women with BMI ≥30 kg/m^2 (22). To further evaluate BMI with respect to these findings, we replicated the four-level stratification scheme of the latter review and found no differences in associations between physical activity and breast cancer risk across the four levels. Whether other measures of adiposity such as weight gain or waist circumference influence associations between physical activity and breast cancer has not been extensively studied. We evaluated but did not find evidence of effect modification by adult weight gain. Unfortunately, waist circumference was not assessed at enrollment of the CPS-II Nutrition cohort; therefore, we were unable to evaluate waist size in relation to the associations of interest.

Results from two other studies suggest that sedentary time may be positively associated with breast cancer risk independent of physical activity (5, 6). Our results do not contribute evidence of such an association. However, our measure of leisure-time sitting may be capturing a different pattern of sedentary behavior than the other studies, which assessed occupational sitting time (6) and routine daily (occupational or otherwise) sitting (5).

Biologic plausibility for the inverse association between physical activity and breast cancer incidence is consistent with the well-established beneficial effects of exercise on endogenous hormone levels, weight control, glucose metabolism, insulin sensitivity, and inflammatory markers, all factors implicated in the etiology of postmenopausal breast cancer (23–25). Thus, physical activity may act favorably upon hormonal and nonhormonal pathways to lower risk of breast cancer.

The major strengths of this study are its large size, prospective design, and availability of detailed exposure information collected prior to breast cancer diagnosis and updated repeatedly during follow-up. It is important to note that the assessment of recreational or leisure-time physical activity in this study may not reflect total physical activity in those working individuals whose occupations involve manual activity. However, most CPS-II women were, or are, homemakers. Furthermore, given the age and demographic of the cohort, any additional contribution of occupational activity to these data is likely to be negligible. This study population is predominantly White, middle-aged or elderly, and well educated; therefore, our results may not be generalizable to populations with different characteristics.

These results contribute additional evidence of a potential benefit of physical activity on the risk of breast cancer in postmenopausal women. Women who engage in at least 7 hours of walking over the course of a week may reap a modest benefit, even in the absence of more vigorous exercise. Given that breast cancer is the most common cancer affecting women (26), and that walking is a common activity among postmenopausal women, the finding of a possible lower risk with an average one or more hours/day of walking is of considerable public health interest.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.S. Hildebrand, S.M. Gapstur, P.T. Campbell, A.V. Patel
Development of methodology: J.S. Hildebrand, P.T. Campbell
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.S. Hildebrand
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Acknowledgments

The authors thank the CPS-II participants and the Study Management Group of the American Cancer Society Epidemiology Research Program for their invaluable contributions to this research. The authors also thank the contribution of central cancer registries supported through the Centers for Disease Control and Prevention (CDC) National Program of Cancer Registries and cancer registries supported by the National Cancer Institute's Surveillance, Epidemiology, and End Results Program.

Grant Support

American Cancer Society funds the creation, maintenance, and updating of the CPS-II cohort.

Received April 17, 2013; revised July 15, 2013; accepted August 1, 2013; published online October 4, 2013.

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Cancer Epidemiol Biomarkers Prev 2013;22:1906-1912.