Early-Life Physical Activity and Postmenopausal Breast Cancer: Effect of Body Size and Weight Change[1]

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Abstract

It is not yet known whether early-life physical activity reduces the risk of developing breast cancer. Subgroup analyses according to menopausal status and body mass may help clarify this association. Data from a population-based case-control study of female residents of Wisconsin, Massachusetts, Maine, and New Hampshire were used to examine associations between body mass and breast cancer risk. Cases ($n = 4614$) were identified by each state's tumor registry; controls ($n = 5817$) were randomly selected from population lists. Frequency of participation in strenuous physical activity when 14–22 years of age, weight at age 18 and 5 years before interview, height, and other factors were ascertained through structured telephone interviews. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were computed using logistic regression. Reductions in postmenopausal breast cancer risk associated with strenuous physical activity were greatest for women in the fourth quartile of body mass index at age 18; the OR for women with the highest activity frequency on average (≥once/day) was 0.45 (95% CI = 0.26–0.79). Associations with frequency of activity also varied by weight change. Compared to women with no activity and little adult weight gain, frequent physical activity was associated with reduced postmenopausal breast cancer risk in women who had lost weight since age 18 (OR = 0.19, 95% CI = 0.05–0.70) or had gained little or modest amounts of weight (weight gain: first tertile, OR = 0.36, 95% CI = 0.05–0.85; second tertile, OR = 0.31, 95% CI = 0.14–0.66). Weighted MET score analyses yielded similar but less inverse results. These findings suggest that the reduced risk of postmenopausal breast cancer associated with frequent, early-life physical activity may be greatest in women who, over the adult years, either lost weight or gained only modest amounts.

Introduction

Most epidemiological studies of physical activity report a reduction in the risk of breast cancer, although the results are not completely consistent (1, 2). In a prospective study of Norwegian women, Thune *et al.* (3) observed that the reduced risk of breast cancer associated with higher levels of recreational physical activity during midlife was greatest in lean women. This finding suggests that analyses in subgroups defined by measures of body mass may provide a clearer understanding of the role of physical activity in the prevention of postmenopausal breast cancer where the adverse effects of obesity are observed (4). High levels of energy expenditure have been correlated with a lower percentage of adipose tissue (5–9), the primary source of endogenous estrogen after menopause (10). Thus, simultaneous examination of body mass, physical activity, and breast cancer risk may help elucidate the mechanisms underlying an inverse association.

The purpose of this report is to expand on our previous observation of a reduced risk of breast cancer associated with regular, moderate-to-strenuous activity in early life (11) by evaluating whether reductions in postmenopausal breast cancer risk depend on body size at age 18 and at interview.

Materials and Methods

Study Participants and Design. Detailed descriptions of this case-control study have been reported (11). Briefly, all female residents ages 20–74 years of Wisconsin, Massachusetts (excluding metropolitan Boston), Maine, and New Hampshire who had a new diagnosis of invasive breast cancer were potentially eligible for this study. Case women were identified by each state's cancer registry from April 1988 through December 1991, except for New Hampshire, where women were enrolled beginning in January 1990. Eligibility was limited to women with listed telephone numbers and drivers' licenses (if less than 65 years of age). Of the 8532 eligible cases, physicians refused contact for 709 cases (8.3%); 464 cases (5.4%) were deceased, 69 cases (0.8%) could not be located, and 402 cases (4.7%) refused to participate. The overall response rate for cases was 80.7%.

Control subjects were randomly selected from the community using two sampling frames: (*a*) women less than 65 years of age were selected from lists of licensed drivers; and (*b*) women ages 65–74 years were selected from a roster of Medicare beneficiaries compiled by the Health Care Financing

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Administration. Eligible controls had no personal history of breast cancer, a listed telephone number, and, if less than 65 years of age, a driver's license. Of the 11,329 eligible controls, 122 (1.1%) had died, 153 (1.4%) could not be located, and 1,521 (13.4%) refused to participate, leaving 9,529 (84.2%) women for analysis.

Data Collection. A telephone interview elicited information on participation in any strenuous physical activity, reproductive history, personal and family medical history, and demographic factors. Strenuous physical activity or team sport participation was ascertained for two age periods: (*a*) 14 to <18 years; and (*b*) 18–22 years. Interviewers were instructed to include only strenuous activities (above MET[3] 6; Ref. 12) such as basketball, soccer, and swimming as well as labor, but not high school physical education. Up to three strenuous activities and/or sports were recorded for each time period, and for each reported activity, the number of years, the number of months per year, and the frequency of episodes (per day/week/month) of participation were noted. We did not ascertain the length (minutes) of each episode of activity. Information on weight 5 years before interview ("recent weight") and tallest height were obtained. For interviews after August 1988, women were also asked about their weight at age 18.

Statistical Analysis. Women were classified as postmenopausal if they reported natural menopause or bilateral oophorectomy before their reference age, which, for cases, was their age at diagnosis. A comparable reference age for controls was defined as the age at interview minus the average time from diagnosis to interview for the case group within each state (range, 8–21 months). Women who reported hysterectomy alone and with at least one remaining ovary were classified as postmenopausal if their age at surgery was in the highest decile for age at natural menopause in the control group (≥55 years for smokers and ≥56 years for nonsmokers).

The frequencies of episodes of reported strenuous physical activities were summed for each time period (14–18 and 18–22 years) and expressed as the number of times per year subjects engaged in physical activity. Frequency of physical activity was then averaged across the two time periods and categorized into five levels. Each physical activity was classified by the average rate of energy expenditure and defined as the ratio of work metabolic rate to resting metabolic rate (MET score; Ref. 12). Weighted MET scores were also calculated as the frequency of activity for each time period multiplied by the MET scores of each activity (11).

Quartiles of BMI [recent weight (kg)/tallest height (m^2)] were calculated based on the distribution of control subjects. Four levels of weight change (difference between recent weight and weight at age 18) were defined: (*a*) weight loss (weight change < 0); and (*b*) tertiles of weight gain (weight change ≥ 0) based on the distribution of controls.

ORs and 95% CIs were obtained from conditional logistic regression models stratified according to age and state (13). To evaluate the joint effects of physical activity and weight variables, indicator variables representing the joint classification of frequency of activity and BMI at age 18, BMI 5 years before interview (recent BMI), and weight change were constructed. All models were adjusted for parity, age at first birth, age at menarche, family history of breast cancer, education, and age at menopause. Additional adjustment for other variables including smoking or alcohol history and use of exogenous hormones did not materially affect risk estimates. Additionally, weight at age 18 was included when evaluating recent BMI, and BMI at age 18 was included when evaluating associations within weight change strata. Effect modification by BMI at age 18, recent BMI, and weight change was evaluated by examining the difference in the log-likelihood between models with and without interaction terms expressed as the products of continuous variables. Women with missing values for covariates were assigned to unknown categories and retained in all analyses.

Subjects with missing or incomplete information on physical activity (256 cases and 428 controls), menopausal status (260 cases and 378 controls), and weight (recent weight and weight at age 18) or height (219 cases and 312 controls) were excluded, therefore limiting analyses to 6186 cases and 8452 controls. Analyses were further restricted to postmenopausal subjects (4614 cases and 5817 controls) because the adverse effect of obesity was present only in this group (14), and the number of premenopausal cases ($n = 1572$) was too small for separate examination of interactions with high levels of activity.

Table 1 ORs and 95% CIs of postmenopausal breast cancer according to frequency of early life physical activity, BMI, and weight change

	Cases ($n = 4614$)	Controls ($n = 5817$)	OR (95% CI)
Frequency of activity (times/year)[a]			
0	2969	3600	1
1–47	825	1085	0.94 (0.85–1.05)
48–103	368	497	0.93 (0.80–1.08)
104–363	397	531	0.90 (0.78–1.04)
≥364	55	104	0.55 (0.39–0.78)
			P for trend = 0.002
Weighted MET score[b]			
0	2969	3600	1
1–2	561	696	0.95 (0.83–1.08)
3–4	694	957	0.91 (0.81–1.02)
5–12	390	564	0.86 (0.74–0.99)
			P for trend = 0.01
BMI (quartiles)			
BMI at age 18 (kg/m^2)[c]			
<18.6	1191	1451	1
18.7–20.1	1173	1456	0.97 (0.97–1.09)
20.2–21.8	1094	1437	0.89 (0.79–1.00)
>21.8	1156	1473	0.92 (0.82–1.03)
			P for trend = 0.05
Recent BMI (kg/m^2)[c]			
<21.8	1035	1478	1
21.9–23.8	1043	1435	1.06 (0.94–1.19)
23.9–26.5	1147	1438	1.11 (0.99–1.25)
>26.5	1389	1466	1.33 (1.18–1.49)
			P for trend < 0.001
Weight change (kg)[d]			
<0	326	537	0.89 (0.75–1.05)
0–7.3	1181	1710	1
7.4–15.0	1361	1777	1.12 (1.00–1.29)
>15.0	1746	1793	1.40 (1.26–1.56)
			P for trend < 0.001

[a] Physical activity estimates adjusted for BMI at age 18, age at first full-term pregnancy, parity, age at menarche, family history of breast cancer, education, and age at menopause.
[b] Weighted MET score was calculated as the average ratio of work metabolic rate to resting metabolic rate, multiplied by the relative frequency of the specific activities reported by each participant.
[c] BMI estimates adjusted for frequency of physical activity and the other covariates listed above.
[d] Weight change estimates adjusted for frequency of physical activity, BMI at age 18, and the other covariates listed above.

[3] The abbreviations used are: MET, ratio of work metabolic rate to resting metabolic rate; OR, odds ratio; CI, confidence interval; BMI, body mass index.

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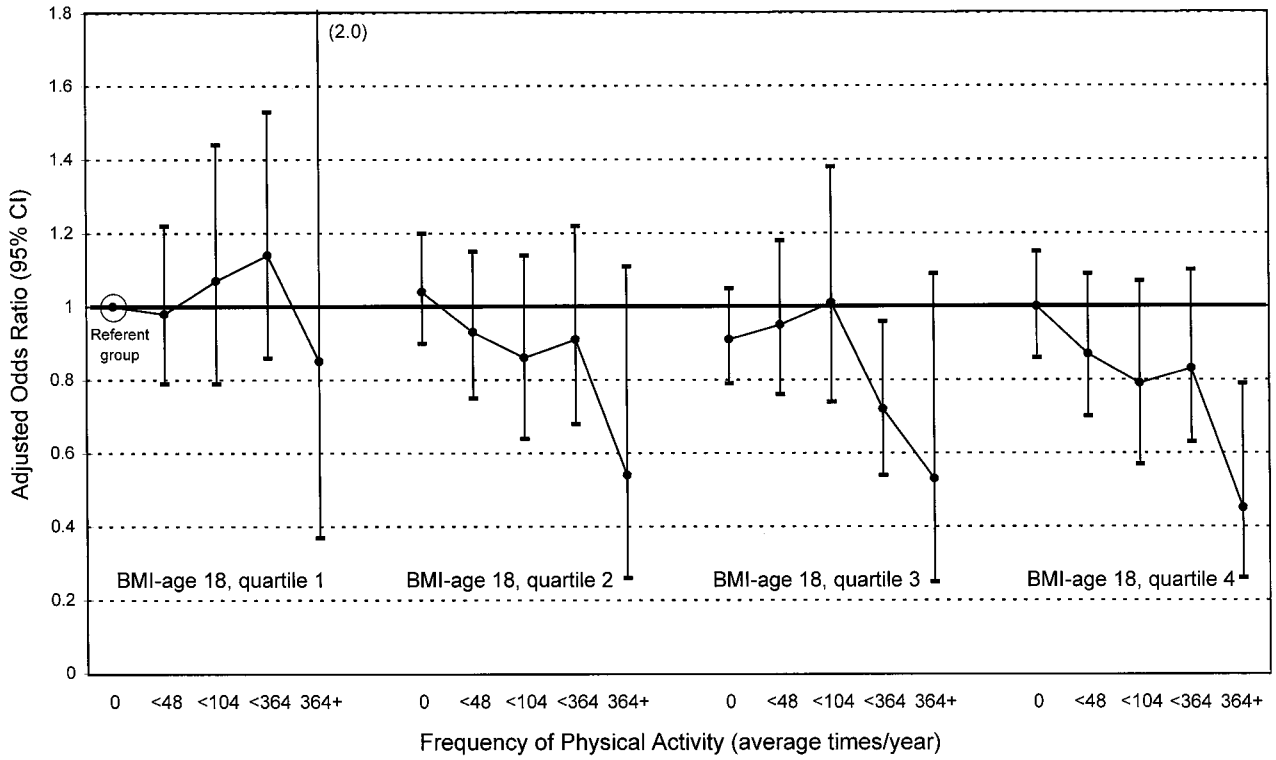

Fig. 1. Adjusted ORs of postmenopausal breast cancer according to BMI at age 18 (*BMI-age 18*) and frequency of physical activity at 14–22 years of age.

Results

Frequent (≥once/day on average) strenuous physical activity at age 14–22 years was associated with up to a 45% reduction in risk of postmenopausal breast cancer (OR = 0.55, 95% CI = 0.39–0.78, *P* for trend = 0.002; Table 1). The association between weighted MET score and risk of postmenopausal breast cancer was not as strong (*P* for trend = 0.01). A weak inverse trend between BMI at age 18 and postmenopausal breast cancer risk was observed (*P* for trend = 0.05), whereas a strong, positive association was observed with recent BMI (*P* for trend < 0.001). Weight change between 18 years of age and 5 years before interview was positively associated with breast cancer risk (*P* for trend < 0.001), with an OR of 1.40 (95% CI = 1.26–1.56) for the highest tertile of weight gain compared to the lowest tertile.

The relationship between strenuous physical activity and risk of postmenopausal breast cancer varied according to BMI at age 18 (Fig. 1; *P* for interaction = 0.02). Reductions in risk were most consistently observed in women with greater BMI at age 18. Compared with subjects in the first quartile of BMI at age 18 who reported no activity, the OR for women in the fourth quartile of BMI at age 18 who exercised on average ≥364 times/year was 0.45 (95% CI = 0.26–0.79). Similar but less strong results were obtained when weighted MET scores were evaluated (*P* for interaction = 0.08).

Associations between strenuous physical activity and postmenopausal breast cancer risk also varied by weight change between age 18 and 5 years before interview (Fig. 2; *P* for interaction = 0.03). Among those who lost weight, the OR for the highest frequency of activity was 0.19 (95% CI = 0.05–0.70) compared to no activity in the first tertile of weight gain. In the first tertile of weight gain, a significantly lower risk of postmenopausal breast cancer was associated with frequent activity (≥364 times/year; OR = 0.36; 95% CI = 0.15–0.85; *P* for trend = 0.001) compared to no activity. In the second tertile of weight gain, a lower risk of breast cancer was observed only with the highest frequency of strenuous activity (OR = 0.31; 95% CI = 0.11–0.66), compared to no activity in the first tertile of weight gain. Strenuous physical activity was not associated with breast cancer risk in the highest tertile of weight gain. Weighted MET score results were again similar but were less strongly inverse (*P* for interaction = 0.3).

Additionally, effect modification of recent BMI on the relationship between frequency of strenuous physical activity and postmenopausal breast cancer was not evident (*P* for interaction = 0.48).

Discussion

Results from this study suggest that the reduced risk of postmenopausal breast cancer associated with frequent episodes strenuous physical activity at 14–22 years of age may be greatest in women who were heaviest within the same time period or who, over the adult years, either lost weight or gained only modest amounts. Among women who were heaviest at age 18, risk of postmenopausal breast cancer was reduced by about 50% in those who exercised frequently.

More pronounced were results obtained from the model examining the joint effects of early-life physical activity and weight change between age 18 and 5 years before interview. Risk of postmenopausal breast cancer was reduced by about 80% among women who were active on a very frequent basis as young adults and who had lost weight between age 18 and 5 years before interview, independent of initial weight. However,

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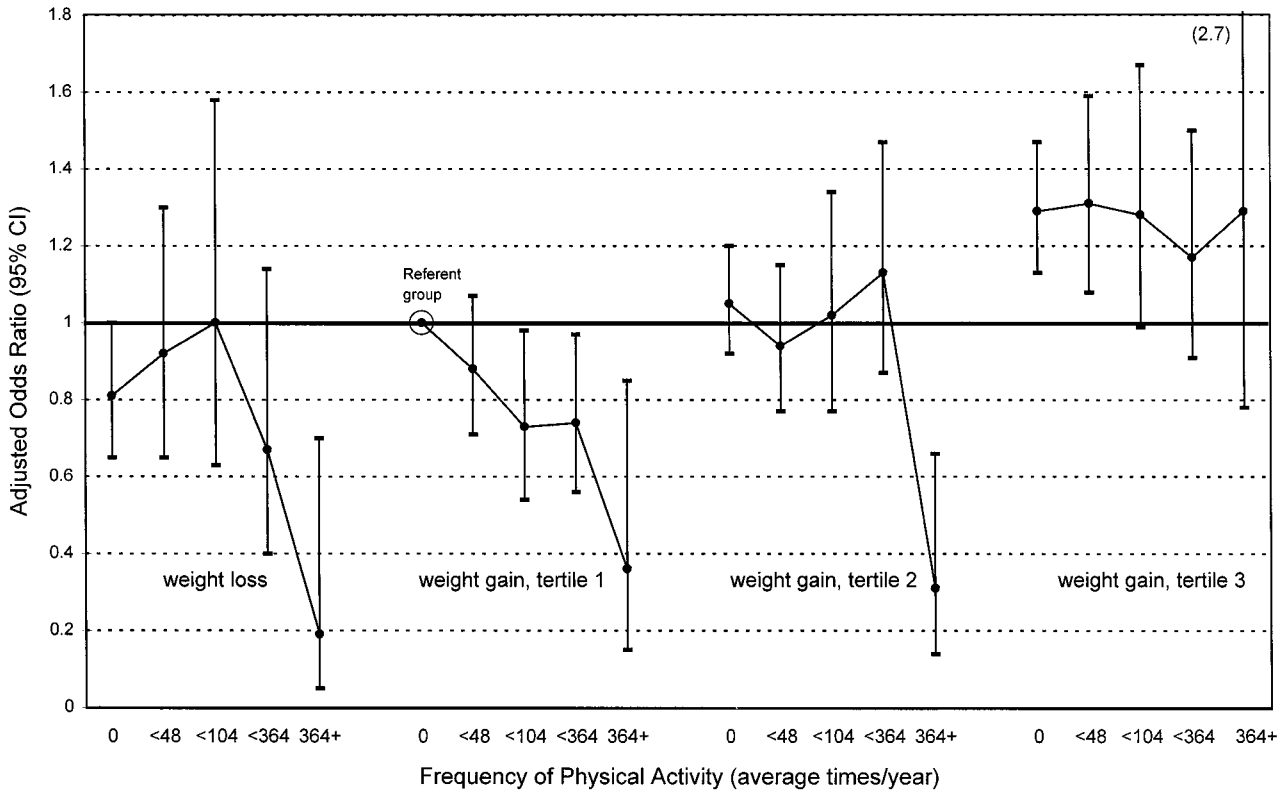

Fig. 2. Adjusted ORs of postmenopausal breast cancer according to weight change (weight at age 18 to recent weight) and frequency of physical activity at 14–22 years of age.

given the small sample size of this subgroup, this estimate is unstable. Interestingly, among women with little lifetime weight gain (first tertile), reduced risk of postmenopausal breast cancer was observed at lower frequencies of early-life activity, a pattern not observed in any other weight change subgroup. In the third tertile of weight gain, all OR estimates were >1.

Limitations of our study should be considered in the interpretation of results. High response rates of cases and controls make substantial selection bias unlikely. Our study's dependence on self-reports of past physical activity and body size makes it susceptible to recall bias (1). However, for a spurious inverse association to occur, physical activity would have to be underreported by cases or overreported by controls. Information was obtained on strenuous physical activity that occurred many years before the interview. Women's reports were reliable; in a reproducibility substudy of 203 women, the Spearman correlation coefficients between frequency of activity in the two interviews was found to be 0.60 (11). Similarly, Spearman correlation coefficients between reports of body size in two interviews indicated excellent reproducibility [weight at age 18, $r = 0.92$; recent weight, $r = 0.92$; height, $r = 0.95$ (14)]. Other studies have reported similar high levels of reliability and, to a lesser extent, validity (15, 16).

Our assessment of physical activity was limited to a single point in time and provided no information on duration or intensity. Whereas sparse data may have constrained our ability to identify a clear dose gradient, incomplete assessment of physical activity may also have contributed. It is possible that the group who exercised in early life and avoided weight gain is enriched with women who were relatively active throughout their lives. Thus, early-life activity may reflect later-life activity in this subgroup. Alternatively, weight gain may reflect inactivity after ages 14–22. A lifetime physical activity history, although challenging to obtain retrospectively, would provide more complete definitions of physical activity (17) and permit a full evaluation of timing of physical activity. We were unable to adjust for the potential confounding effect of later-life physical activity on breast cancer risk. Finally, weight change represents net change over many years; intermittent fluctuations were not assessed, nor was intentionality of weight change.

Evidence regarding an inverse association between activity and breast cancer generally supports a similar effect in postmenopausal women (1). However, the literature is less consistent in the period or periods that are most relevant. Results from two studies (11, 18) provide strong overall support of an inverse association between activity early in life and postmenopausal breast cancer (range, 50–54%), but other studies have not reported similar findings (19–22). The strong and adverse effect of weight gain on postmenopausal breast cancer (4, 14) may obscure any inverse associations between early-life physical activity and risk when evaluating an overall effect. To our knowledge, no studies have specifically evaluated how associations between physical activity during late adolescence/young adulthood and risk of postmenopausal breast cancer may differ according to early-life body size and subsequent weight change. Our results are in general agreement with a prospective study of Norwegian women (3) that included both pre- and postmenopausal women. In that study, Thune *et al.* (3) observed that the reduction in breast cancer risk associated with recreational physical activity, assessed 1 year before baseline,

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was greatest in lean women (baseline BMI < 22.8 kg/m^2). For most subjects in this study, baseline assessment of physical activity and body size was at mid-life. Women in our study who lost weight (median change $= -4.5$ kg) or who gained small amounts (first tertile, median weight gain $= 4.5$ kg) were also the lightest 5 years before interview (median recent BMI $=$ 20.7 and 21.9 kg/m^2, respectively). If the Norwegian women in the first tertile of BMI were similar with respect to net weight change to the women in our study who lost weight or gained little, then the reduced risk of postmenopausal breast cancer in our study is also comparable.

In summary, these current findings suggest that frequent episodes of strenuous physical activity during young adulthood may have the greatest benefit for reducing postmenopausal breast cancer risk among women who avoid substantive weight gain during adult life–a recommendation for general health (23). In postmenopausal women who gain substantive adult weight, the benefits of frequent and strenuous early-life physical activity appear to be lost. Unfortunately, the prevalence of recreational physical activity in this country is low (24, 25), and adult weight gain is increasingly common (26)–behaviors that may have contributed to breast cancer incidence.

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