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Lifetime physical activity and risk of breast cancer

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Summary We conducted a case–control study of 394 women with breast cancer and 788 control women (91% response) to investigate the association of lifetime physical activity with mainly menopausal breast cancer risk. After controlling for potential confounders, the odds ratios (95% confidence intervals) for increasing quartiles of lifetime physical activity were 1.00 (referent), 0.91 (0.60–1.37), 0.91 (0.60–1.39), and 1.10 (0.73–1.67), respectively; *P*, trend = 0.47. We also separately examined physical activity at ages 12–18, 19–34, 35–49 and ≥50 years; no significant trends were observed in any age group. These data do not support a role of physical activity in preventing breast cancer. © 2001 Cancer Research Campaign http://www.bjcancer.com

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Breast cancer is the most common cancer occurring among women in Western countries. Unfortunately, almost all established risk factors for this disease (e.g., age at first childbirth or a family history of breast cancer) are not easily altered. One modifiable risk factor that holds promise for prevention is physical activity. Physical activity can modulate levels of female reproductive hormones and influence menstrual characteristics Bernstein et al, 1987). Additionally, active women are more likely to be lean, which is associated with a lower risk of postmenopausal breast cancer (Huang et al, 1997).

However, epidemiologic studies of physical activity and breast cancer risk have yielded inconsistent findings (Gammon et al, 1998a). While several studies have reported lower rates of breast cancer among physically active women than sedentary women (Bernstein et al, 1994; Thune et al, 1997), other studies have not (Dorgan et al, 1994; Rockhill et al, 1998). One reason for this could be the assessment of physical activity at different time periods in a woman's life. The critical time period for physical activity to reduce breast cancer risk may be throughout the life span. Few studies have investigated lifetime physical activity and breast cancer risk. To provide more information, we conducted a case–control study within the Women's Health Study.

MATERIALS AND METHODS

Subjects

The Women's Health Study is an ongoing clinical trial testing low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among 39 876 apparently healthy female health professionals throughout the United States (Buring and Hennekens, 1992; Rexrode et al, 2000). After an average follow-up of 48 months (February 1998), 411 women developed breast cancer, confirmed by medical records.

At the time we initiated the present case–control study (October 1999), 17 women with breast cancer had died. The remaining 394 women were enrolled as cases in the present study. For each case, we selected 2 controls free of breast cancer at the time the case developed breast cancer, matched to cases on age and date of randomization into the Women's Health Study. The present study was conducted after approval by the institutional review board of Brigham and Women's Hospital. We mailed a questionnaire on physical activity to the 394 cases and 788 controls, and after up to 4 mailings and 2 telephone calls, received questionnaires from 364 cases (92%) and 715 controls (91%).

Assessment of physical activity

A previously developed physical activity questionnaire was used (Kriska et al, 1988; Pereira et al, 1997), which considers 4 age periods: 12–18, 19–34, 35–49 and ≥ 50 years. For each age period, women were asked to list their leisure-time physical activities. For every activity in each of the 4 age periods, they were asked to report the number of years, months per year, and hours per week the activity was carried out in that age period. This questionnaire, administered 2–3 months apart to postmenopausal women, yielded Spearman correlation coefficients of 0.69–0.85 for the various ages (Kriska et al, 1988).

We estimated the average energy expenditure in MET-hours per week (1 MET-hour = energy expended while sitting quietly for one hour) for each of the 4 age periods (Pereira et al, 1997). We then estimated average lifetime physical activity by calculating a weighted average of the energy expended during the 4 age periods, with the weighting factor being the number of years in the time period (e.g., 7 for the time period 12–18 years). Physical activity was estimated up to the time of entry into the Women's Health Study (i.e., prior to the development of breast cancer for cases).

Data analyses

We conducted conditional logistic regression to analyse the association between physical activity and risk of breast cancer (Breslow

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and Day, 1980). Women were categorized into quartiles of physical activity for each of the 4 age periods, as well as for lifetime physical activity, based on the distribution among controls. We calculated 95% confidence intervals for the estimated relative risks and used 2-tailed tests to calculate *P* values for trend. We also conducted unconditional logistic regression (Breslow and Day, 1980), controlling for the matching factors of age and date of randomization. Because the results from both analyses were similar, we present findings only from the unconditional logistic regression analyses.

We made multivariate analyses, to control for potential confounders, additionally adjusting for randomized treatment assignment, body mass index (continuous variable), alcohol consumption (rarely, 1–3 drinks/month, 1–6/week, ≥ 1/day), age at menarche (≤ 10, single year increments, ≥ 16 years), number of pregnancies lasting ≥ 6 months (none, 1, single unit increments, ≥ 6), age at first pregnancy lasting ≥ 6 months (never pregnant, < 20, 5-year increments, ≥ 35 years), menopausal status (premenopausal, postmenopausal, not sure), ever use of oral contraceptives (no, yes), postmenopausal hormone use (never used, past use, current use), and history of breast cancer diagnosed before age 60 in either mother or sister (no, yes). Information on these variables was obtained from the baseline questionnaire that women completed at entry into the Women's Health Study (i.e., prior to the development of breast cancer in cases).

RESULTS

Table 1 presents the characteristics of women studied. Cases and controls were matched on age; their mean age at the time of entry into the present study was 56 years. The distribution of physical activity was skewed, with a long tail towards higher values. Among cases, the median value of the average amount of physical activity carried out over the lifetime was 17.5 MET-hours (approximately equivalent to 4–5 hours of brisk walking) per week. Among controls, this was similar, at 17.2 MET-hours per week. When we examined physical activity separately at ages 12–18, 19–34, 35–49 and ≥ 50 years, cases and controls did not differ. Both groups of women were similar with regard to body mass index, postmenopausal status, current use of postmenopausal hormones (among postmenopausal women), and ever use of oral contraceptives. As expected, the following risk factors for breast cancer were present at a higher prevalence among cases: heavy alcohol use, menarche at a younger age, nulliparity and a family history of breast cancer.

We first examined the association between lifetime physical activity, with women categorized into quartiles according to the distribution among controls and risk of breast cancer (Table 2). In analyses that adjusted only for the matching factors of age and date of randomization, we found no association between lifetime physical activity and risk. The most active quartile of women had a similar risk of breast cancer as the least active (odds ratio [OR], 1.04; 95% confidence interval (CI), 0.73–1.48). Additional adjustment for randomized treatment assignment, body mass index, alcohol consumption, menstrual and reproductive characteristics, use of oral contraceptives and postmenopausal hormones, and family history of breast cancer did not materially change the findings (OR, 1.10; 95% CI, 0.73–1.67).

We then examined physical activity separately for the 4 age periods. Physical activity was not clearly predictive of lower risk of breast cancer in any of these age periods (Table 2).

Since previous studies have suggested that the association of physical activity with breast cancer risk may differ among women who are lean or overweight, and among pre- and postmenopausal

Table 1 Characteristics of cases and controls

Characteristic	Cases (*n* = 364)	Controls (*n* = 715)
Mean age (SD), years	56.0 (7.6)	56.0 (7.5)
Median physical activity, MET-hr/week		
At age 12–18	17.0	16.9
At age 19–34	7.8	8.7
At age 35–49	15.6	16.6
At age ≥ 50	21.1	22.2
Lifetime[a]	17.5	17.2
Mean body mass index (SD), kg/m^2	25.1 (4.0)	25.8 (4.8)
Alcohol consumption, %		
Rarely	40.4	42.4
Monthly	11.0	12.2
Weekly	35.7	34.1
Daily	12.9	11.4
Menarche ≥ 14 years, %	17.3	19.2
Nulliparous, %	14.1	8.7
Postmenopausal, %	63.9	64.6
Postmenopausal hormone use[b], %		
Never	28.5	26.8
Past	12.9	15.6
Current	58.6	57.6
Ever used oral contraceptives, %	63.5	64.8
Family history of breast cancer[c], %	9.2	5.0

[a]Weighted average of physical activity during ages 12–18, 19–34, 35–49 and ≥ 50 years.
[b]Among postmenopausal women. [c]In mother or sister, with onset < 60 years.

Table 2 Odds ratios (OR) and 95% confidence intervals (CI) of breast cancer, according to physical activity

Physical activity level	Median, MET-h/wk	No. of cases	No. of controls	'Crude' OR[a] (95% CI)	Multivariate OR[b] (95% CI)
Lifetime[c]					
Quartile 1	3.0	92	177	1.00 (referent)	1.00 (referent)
Quartile 2	11.3	88	182	0.93 (0.65–1.33)	0.91 (0.60–1.37)
Quartile 3	23.7	89	181	0.94 (0.66–1.35)	0.91 (0.60–1.39)
Quartile 4	52.9	95	175	1.04 (0.73–1.48)	1.10 (0.73–1.67)
				P, trend = 0.70	*P*, trend = 0.47
12–18 years					
Quartile 1	0	100	169	1.00 (referent)	1.00 (referent)
Quartile 2	8.8	81	189	0.72 (0.50–1.03)	0.62 (0.41–0.95)
Quartile 3	27.5	99	171	0.98 (0.69–1.39)	0.80 (0.53–1.20)
Quartile 4	70.5	84	186	0.76 (0.53–1.09)	0.82 (0.54–1.24)
				P, trend = 0.37	*P*, trend = 0.90
19–34 years					
Quartile 1	0	99	170	1.00 (referent)	1.00 (referent)
Quartile 2	4.7	86	184	0.80 (0.56–1.14)	0.79 (0.52–1.20)
Quartile 3	14.4	88	182	0.82 (0.58–1.18)	0.82 (0.54–1.24)
Quartile 4	47.2	91	179	0.87 (0.61–1.24)	0.84 (0.55–1.27)
				P, trend = 0.80	*P*, trend = 0.68
35–49 years					
Quartile 1	0	99	170	1.00 (referent)	1.00 (referent)
Quartile 2	9.2	89	181	0.84 (0.59–1.20)	0.79 (0.52–1.20)
Quartile 3	23.5	84	186	0.77 (0.54–1.10)	0.68 (0.45–1.04)
Quartile 4	57.5	92	178	0.88 (0.62–1.25)	0.81 (0.53–1.23)
				P, trend = 0.66	*P*, trend = 0.50
≥ 50 years					
Quartile 1	2.8	72	130	1.00 (referent)	1.00 (referent)
Quartile 2	15.0	66	137	0.88 (0.58–1.32)	0.72 (0.44–1.20)
Quartile 3	31.5	54	148	0.66 (0.43–1.01)	0.56 (0.34–0.93)
Quartile 4	66.7	76	127	1.08 (0.72–1.62)	1.04 (0.64–1.70)
				P, trend = 0.58	*P*, trend = 0.52

[a]From unconditional logistic regression, adjusted for the matching factors of age and date of randomization into the Women's Health Study. [b]Additionally adjusted for randomized treatment, body mass index, alcohol consumption, age at menarche, age at first pregnancy lasting ≥ 6 months, number of pregnancies lasting ≥ 6 months, menopausal status, ever use of oral contraceptives, use of postmenopausal hormones, and family history of breast cancer. [c]Weighted average of physical activity during ages 12–18, 19–34, 35–49 and ≥ 50 years.

women, we examined interactions with body mass index and postmenopausal status. In multivariate analyses, there was no significant interaction with either (*P*, interaction = 0.76 and 0.55, respectively).

DISCUSSION

These data do not support the hypothesis that physically active women experience lower rates of breast cancer. We did not observe decreased rates of breast cancer among women who were physically active throughout their life from age 12 onwards, or among women who were active at different ages.

Few previous studies have investigated lifetime physical activity in relation to breast cancer risk. Several studies have assessed physical activity at different ages, but did not combine these measures to estimate lifetime physical activity (D'Avanzo et al, 1996; Gammon et al, 1998b; Levi et al, 1999; Morardi et al, 2000). Only 3 studies have integrated assessments of physical activity at different ages in a woman's life to examine the association of lifetime physical activity with breast cancer risk (Bernstein et al, 1994; Carpenter et al, 1999; Verloop et al, 2000). All 3 studies reported lower breast cancer risk among women who were physically active throughout their life from adolescence, with risk reductions of 33% to 58% among the most active women.

Our findings are in contrast with these 3 other studies. It is unclear why the present findings differ. While 2 of the studies examined women who were younger than those in the present study (≤ 40 in Bernstein et al, 1994; and 20–54 years in Verloop et al, 2000), one investigated women of similar age (Carpenter et al, 1999). The questionnaires used to assess lifetime physical activity in these other studies also differed from our questionnaire. Could imprecise assessment of physical activity in our study explain the inconsistency? We believe this is unlikely. The questionnaire we used has good reliability (Kriska et al, 1988) and has face validity. It is extremely difficult to directly validate lifetime physical activity. Based on this instrument, cases and controls had similar levels of physical activity; they also had similar body weight. Both groups of women reported the lowest levels of physical activity between ages 19 and 34 years, and higher levels thereafter. This pattern is consistent with trends in activity in national surveys of US women (US Department of Health and Human Services, 1996). Finally, physical activity levels among women in this study are similar to those among postmenopausal women in another study where physical activity was assessed using the same questionnaire (Kriska et al, 1988).

It is unlikely that the women in the present study were insufficiently active to show effects on breast cancer risk. In 2 studies of lifetime physical activity, women who exercised at least 3.8 hours (Bernstein et al, 1994) or 17.6 MET-hours (approximately equivalent to 4–5 hours of brisk walking) a week (Carpenter et al, 1999) experienced lower breast cancer risk. This level of activity was achieved by about half the women in the present study (median level in controls was 17.2 MET-hours per week).

Lack of statistical power may partly explain the present findings, if the effect of physical activity on breast cancer risk is small to moderate. The 95% confidence interval for the odds ratio of breast cancer among women in the most active quartile of lifetime physical activity in this study, 0.73–1.67 (Table 2), was compatible with up to a 27% reduction in risk. All 3 previous studies of lifetime physical activity observed higher risk reductions (Bernstein et al, 1994; Carpenter et al, 1999; Verloop et al, 2000). However, another large study of physical activity in middle-age and older women reported a risk reduction of only 20% among the most active fifth of women (Rockhill et al, 1999). The present study would not have sufficient statistical power to detect this small difference.

In conclusion, while it is biologically plausible for physically active women to experience lower risk of breast cancer, the present study does not support this hypothesis. Nevertheless, physical activity should still be promoted among women, since it reduces the risk of many chronic diseases, such as coronary heart disease (US Department of Health and Human Services, 1996).

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