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Physical Activity and Risk of Breast Cancer in the Framingham Heart Study

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The authors analyzed data from the Framingham Heart Study to evaluate the association between physical activity and breast cancer risk. Physical activity was ascertained by a physician-administered questionnaire from 2,321 women at the fourth biennial examination conducted in 1954–1956. Breast cancers were identified by self-report, surveillance of admissions to Framingham Union Hospital, and review of death records; all but one were histologically confirmed. During 28 years of follow-up, 117 breast cancer cases were diagnosed among the 2,307 women with data on physical activity and reproductive history (a potential confounder). Analysis was performed using Cox proportional hazards models with age as the underlying time variable. Models were adjusted for age at physical activity assessment, menopausal status, age at first pregnancy, parity, education, occupation, and alcohol ingestion. We observed a gradient of increasing risk of breast cancer with increasing physical activity (trend $p = 0.06$). The relative risk for women in the highest versus lowest activity quartile was 1.6 (95% confidence interval 0.9–3.0; $p = 0.13$). Although both moderate-to-heavy leisure and occupational activities were associated with an increased risk, the association was marginally significant only for leisure activity ($p = 0.06$). Our findings do not support a protective effect of physical activity during adulthood for breast cancer, but suggest an increased risk among more active women. *Am J Epidemiol* 1994;139:662–9.

breast neoplasms; exercise; prospective studies

Physical activity has been hypothesized to protect against breast cancer. Frisch et al. (1) first proposed a protective effect after observing a lower prevalence of breast cancer among former college athletes compared with nonathletes in a cohort of 5,398 living alumnae (relative risk = 0.5; 95 percent confidence interval (CI) 0.3–1.0). Paffenbarger et al. (2), however, failed to detect an association of breast cancer with participation in sports during the early college years. A nonsignificant inverse association between self-reported activity and postmenopausal breast cancer was observed for participants of the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (3). Relative risks for the most active versus least active women were 0.6 (95 percent CI 0.3–1.2) and 0.7 (95 percent CI 0.4–1.4), respectively, for recreational and nonrecreational activities. There was, however, a suggestion of an increased risk of premenopausal breast cancer among the more active women in this cohort. Occupational activity, surmised on

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Abbreviation: CI, confidence interval.

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the basis of job titles, also was related to a decreased risk of dying from breast cancer in Washington State (4). Among women whose usual lifetime occupation was classified as nonsedentary, the observed number of all deaths attributed to breast cancer was significantly less than expected (proportionate mortality ratio = 85).

The Framingham Heart Study is a prospective cohort study of cardiovascular risk factors that includes data on physical activity at work and during leisure time as well as breast cancer incidence. Physical activity data were collected at the fourth biennial Framingham examination, and breast cancer ascertainment is complete through the 18th examination. We analyzed the relation between physical activity and the development of breast cancer during these 28 years of follow-up.

MATERIALS AND METHODS

The Framingham Heart Study started in 1948. The cohort, which initially included 2,873 women, was followed with biennial examinations for 34 years (examinations 1–18) with less than 3 percent loss to follow-up. At the fourth biennial examination, conducted in 1954–1956, self-reports of physical activity were obtained from 2,321 women aged 35–68 years. Data were missing for 55 women who died before the examination, 286 who missed the examination, and 211 who took the examination but did not report physical activity.

The methods used to identify cancers in the cohort have been described in detail by Kreger et al. (5). Briefly, the cases initially were identified by self-report at examinations, surveillance of admissions to Framingham Union Hospital, and review of all death records. Through 1988, primary breast cancer (*International Classification of Diseases* code 174 (6)) was diagnosed in 164 women. Histologic confirmation was obtained for all but one woman who had a growing mass in her breast but did not undergo surgery. After excluding 16 breast cancer cases diagnosed prior to examination 4, 27 that occurred among women who missed examination 4 or did not report physical activity at the examination, and three cases diagnosed after the last visit for which we have complete follow-up (examination 18), 118 cases remained. One of these potential cases and 13 noncases were dropped prior to analysis because they were missing data on reproductive history, leaving a total of 117 cases and 2,181 noncases.

Physical activity was assessed by a physician-administered questionnaire that ascertained how many hours a day a woman usually spent at sleep and rest and, during work and leisure time, at sedentary (e.g., standing), slight (e.g., walking), moderate (e.g., greater than walking but less than running), and heavy (e.g., running) activities. The hours at each level of activity, weighted by the relative oxygen consumption for that activity, were summed to create a physical activity index (7). Activity level weights were the following: 1) sleep and rest, 1.0; 2) sedentary, 1.1; 3) slight, 1.5; 4) moderate, 2.4; and 5) heavy, 5.0.

For analysis, women were classified as premenopausal if they were still having periods or as postmenopausal if their periods had stopped naturally or as a result of radiation treatment, hysterectomy with bilateral oophorectomy, or hysterectomy without bilateral oophorectomy if 60 or more years old. Women who were less than 60 years old and who had a hysterectomy without bilateral oophorectomy were treated as a separate group because their menopausal status in terms of hormones was unknown. Women for whom data on menopausal status were missing were treated as postmenopausal if they were 60 or more years old and as having unknown menopausal status if they were less than 60.

Univariate comparisons for continuous variables were evaluated by the Wilcoxon two-sample test with a correction for continuity and for categorical variables by the chi-square test (8). Age-adjusted and multivariate analyses were performed using Cox proportional hazards, with age as the underlying time variable in the model (9). For

multivariate analyses, a stratum was created for each case that included all women within 2 years of age of the case at the time physical activity was measured, of the same parity and menopausal status as the case at the age she developed breast cancer, and alive and free of breast cancer at the age the case was diagnosed. The same woman could be included in more than one stratum, and women who developed breast cancer could be included as noncases for cases diagnosed at a younger age. Adjustment was made for age at first pregnancy, education, occupation, and alcohol ingestion (ascertained at examination 2) by including these variables as covariates in the model with physical activity. The occupational classification system of the *1970 Census of the Population* (10) was used to categorize current jobs reported at examination 4. Education and alcohol ingestion also were treated as categorical variables, whereas age at first pregnancy was continuous. Weight, height, body mass index, and postmenopausal exogenous hormone use did not substantially affect results and were not included in models. SAS statistical software was used for all analyses (11).

We used two approaches to model the relation of physical activity to breast cancer. First, women were categorized into quartiles on the basis of their physical activity index and, using dummy variables, risks were estimated relative to the lowest quartile including the most sedentary women. The significance of the trend in risk was evaluated by including the physical activity index in the model as a continuous variable. Second, we combined the hours spent at sedentary and slight activity into a single variable and moderate and heavy activity into another variable and included these two variables in a model with the hours at sleep and rest as the referent. Thus, we estimated the risk due to replacing 1 hour per day of sleep/rest with 1 hour of sedentary-to-slight or moderate-to-heavy activity. To investigate whether the risk differed for leisure and occupational activity, we created separate variables for the hours spent at sedentary-to-slight and moderate-to-heavy leisure and occupational activity and included these four variables in a model with hours at sleep/rest as the referent.

RESULTS

The characteristics of 117 breast cancer cases and 2,181 noncases are shown in table 1. At the time of diagnosis, five cases were premenopausal, 106 were postmenopausal, and six had an unknown menopausal status. Consistent with established breast cancer risk factors (12), cases were significantly older at the time of their first pregnancies and had significantly fewer pregnancies. As expected, cases also were more likely to have graduated from high school (13), although their distribution of years of education did not differ significantly from that of noncases, and they were no more likely to be employed in professional and managerial occupations. Body size, which has been positively associated with postmenopausal breast cancer in some (14–16) but not in all (17, 18) studies, was not related to breast cancer in this population. Contrary to most published reports (12), alcohol ingestion was slightly inversely associated with risk.

All women spent at least some time each day sleeping or resting; the median was 8 hours/day (range, 4–13 hours) and did not differ between cases and noncases. Essentially all women (99 percent) also spent time in sedentary and slight activities, and the amount of time spent in these activities did not differ for cases and noncases. Cases spent a median of 8 hours/day (range, 0–16 hours) in sedentary and 6 hours/day (range, 0–14 hours) in slight activities. Noncases spent a median of 7 hours/day (range, 0–18 hours) in sedentary and 7 hours/day (range, 0–16 hours) in slight activities. Eighty-five cases (73 percent) and 1,442 noncases (66 percent) were involved in activities that require moderate levels of exertion. The median time per day spent at moderate levels of activity was 1 hour for both cases (range, 0–10 hours) and noncases (range, 0–14 hours). Only six cases (5 percent) and 121 noncases (6 percent) were involved in heavy

TABLE 1. Characteristics of breast cancer cases and noncases in the Framingham Heart Study (1954–1984)

	Age (years) at examination 4		Body mass index (kg/m²) at examination 4		Height (cm) at examination 4		Age (years) at menopause		Age (years) at first pregnancy		Parity							
											0		1–2		3–4		≥5	
	Median	5–95th percentile	Median	5–95th percentile	Median	5–95th percentile	Median	5–95th percentile	Median	5–95th percentile	No.	%	No.	%	No.	%	No.	%
Cases (n = 117)	50	38–63	24.9	20.3–31.8	63.0	59.0–66.0	48	39–54	27	19–38	40	34	48	41	23	19	7	6
Noncases (n = 2,181)	49	38–64	25.1	20.0–34.6	62.0	58.0–66.0	48	36–54	25*	19–35	520	24*	852	39	593	27	215	10

TABLE 1. Continued.

	Education										Occupation												Alcohol (oz/month)† at examination 2							
	Grade school only		Some high school		High school graduate		Business technical school		College		Housewife		Professional, technical, managerial		Sales		Clerical		Craftsmen, operatives, laborers		Service workers		0		1		2–9		≥10	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cases (n = 117)	27	23	10	9	47	41	15	13	16	14	42	38	11	10	6	5	24	22	18	16	10	9	50	43	31	27	16	14	18	16
Noncases (n = 2,181)	608	29	278	13	652	31	264	12	321	15	905	44	203	10	110	5	257	12	370	18	214	10	850	40	436	21	389	18	429	20

* $p < 0.01$.
† One ounce (oz) = ~30 ml.

activities. The maximum number of hours spent per day in heavy activities was 6 hours for cases and 4 hours for noncases.

Women were followed for a median of 26 years, contributing a total of 54,000 person-years of follow-up. The numbers of person-years and breast cancer cases by quartiles of the physical activity index are shown in table 2. There was no evidence for an association in these unadjusted data; the risks relative to the first (lowest) quartile of activity were 1.1, 1.0, and 1.1 for the second through fourth (highest) quartiles, respectively. As shown in table 3, after adjustment for age, women in the upper quartiles of activity were at an increased risk of breast cancer. Further adjustment for other potential confounders, primarily reproductive and socioeconomic, smoothed the gradient of increasing risk of breast cancer with increasing physical activity. The risk for women in the highest quartile of physical activity was 60 percent higher than that for women in the lowest quartile, and the risks for women in the two middle quartiles were intermediate. The test for trend from the multivariate model was marginally significant ($p = 0.06$).

Because few women participated in strenuous activities, the number of hours spent at heavy activity was combined with the number of hours spent at moderate activity to examine the association of each activity level with breast cancer risk. Sedentary and slight activity did not differ in their association with breast cancer and were combined for presentation. The relative risks for leisure and occupational activities, separately and in combination, are presented in table 4. Although both leisure and occupational moderate-to-heavy activities were related to an increased breast cancer risk, the association was marginally significant only for leisure activity ($p = 0.06$), such that each hour spent daily in moderate-to-heavy leisure activities instead of at sleep/rest was associated with an increased risk of 20 percent.

Results were comparable when we excluded six cases diagnosed within 1 year of examination 4 when physical activity was assessed. When we restricted analysis to postmenopausal breast cancer, the results also were similar although trends were less consistent.

TABLE 2. Number of breast cancer cases by quartile of the physical activity index* in the Framingham Heart Study (1954–1984)

Physical activity index by quartile†	Women	Person-years	Breast cancer cases
1 (low)	488	10,671	22
2	673	15,268	35
3	554	13,347	28
4 (high)	583	13,813	32

* Physical activity index = sleep/rest hours × 1.0 + sedentary hours × 1.1 + slight activity hours × 1.5 + moderate activity hours × 2.4 + heavy activity hours × 5.0.

† Quartile cutpoints: 1 = 25–28, 2 = 29–30, 3 = 31–32, 4 = 33–54.

DISCUSSION

Physical activity was not associated with a reduced risk of breast cancer in this cohort; if anything, the results suggest a positive relation. The reason for this finding is unclear. The majority of epidemiologic studies have found an inverse (1, 4) or null (2) association between physical activity and breast cancer in women. The only other published report of a positive relation was for premenopausal breast cancer in the study by Albanes et al. (3), in which the most active women had a nonsignificant, increased risk. These women, however, had a nonsignificant, lower risk of postmenopausal breast cancer. In our study, the vast majority of cases (91 percent) occurred among postmenopausal women. Although most animal studies indicate that there is a protective effect of exercise on mammary carcinogenesis (18–21), the enhancement of mammary carcinogenesis in rats by moderate aerobic exercise also has been reported (22, 23).

Strenuous physical activity is associated with an increase in luteal phase defects and anovulation (24–26), and depressed blood estradiol levels (26–30) have been reported for amenorrheic athletes. Recreational and

TABLE 3. Relative risk of breast cancer by quartile of the physical activity index* in the Framingham Heart Study (1954–1984)

Physical activity index by quartile†	Age-adjusted model‡			Full model§		
	Relative risk	95% CI‖	p value	Relative risk	95% CI	p value
1 (low)	1.0			1.0		
2	1.3	0.7–2.2	0.38	1.2	0.7–2.1	0.52
3	1.3	0.7–2.3	0.37	1.3	0.7–2.4	0.39
4 (high)	1.5	0.8–2.6	0.16	1.6	0.9–2.9	0.13

* Physical activity index = sleep/rest hours × 1.0 + sedentary hours × 1.1 + slight activity hours × 1.5 + moderate activity hours × 2.4 + heavy activity hours × 5.0.
† Quartile cutpoints: 1 = 25–28, 2 = 29–30, 3 = 31–32, 4 = 33–54.
‡ Relative risks from a proportional hazards model with age as the underlying time variable.
§ Relative risks from a proportional hazards model with age as the underlying time variable, stratifying on age at examination 4, number of pregnancies, and menopausal status and including age at first pregnancy, education, occupation, and alcohol ingestion as covariates.
‖ CI, confidence interval.

TABLE 4. Relative risk of breast cancer related to replacing 1 hour of sleep/rest daily with 1 hour of leisure or occupational activity at the specified level in the Framingham Heart Study (1954–1984)

Activity	Relative risk*	95% CI†	p value
Leisure			
Sedentary to slight	1.1	0.9–1.3	0.47
Moderate to heavy	1.2	1.0–1.6	0.06
Occupational			
Sedentary to slight	1.0	0.8–1.2	0.99
Moderate to heavy	1.1	0.9–1.3	0.50
Total			
Sedentary to slight	1.0	0.9–1.2	0.63
Moderate to heavy	1.1	0.9–1.3	0.22

* Relative risks from two proportional hazards models with age as the underlying time variable, stratifying on age at examination 4, number of pregnancies, and menopausal status and including age at first pregnancy, education, occupation, and alcohol ingestion as covariates. In the first model, hours at leisure and occupational activity were specified separately, and in the second model they were combined to provide an estimate for total activity.
† CI, confidence interval.

submaximal activities also have been associated with disturbed ovarian function (31) and alterations in serum hormone levels (31–37). At submaximal levels, the effect of acute endurance exercise on serum hormones depends on the intensity and duration of exercise and the woman's conditioning, and transient decreases (37) and increases (32–36) in blood estrogen levels have been reported. Resting serum estradiol levels were lower in recreational athletes compared with those in sedentary women in a cross-sectional study (31). In a prospective study (38), however, 1 year of moderate aerobic training did not alter the serum estradiol levels significantly from those at baseline.

Most of the women in our cohort did not participate in strenuous activities. Those who were active generally participated in activities with moderate intensity levels (defined as activities requiring effort greater than walking but less than running). It is likely that such moderate activity in our cohort, if anything, would have lowered basal serum estrogen levels. Since estrogens are believed to enhance the development and growth of breast cancers (39), an endocrine mechanism does not readily explain the slightly higher risk of breast cancer that we observed in more active women.

Free radicals damage DNA and may play a role in carcinogenesis (40). Although physical activity results in the generation of free radicals (41), the significance of this effect in human cancer is unclear. If it were important, a positive association between physical activity and cancer at numerous sites would be expected. However, physical activity has been reported to have a null or inverse association with cancer at most sites (2, 3, 42).

Active women differ from sedentary women in numerous characteristics (43), and physical activity in our cohort could be related to breast cancer indirectly through its correlation with one or more other traits. Although we adjusted our analyses for the major breast cancer risk factors except family

history, which was unavailable, a substantial portion of breast cancers cannot be accounted for by known risk factors (44). Furthermore, we were unable to adjust for any dietary differences that may have existed between active and sedentary individuals. Physical activity has been reported to alter some individuals' food consumption (45), and diet has been hypothesized to be associated with breast cancer by some investigators (46) but not others (47).

The questionnaire used in this study grouped activities by intensity level and ascertained the number of hours per day usually spent at each level. The questionnaire may not have been accurate enough to correctly classify participants by physical activity level. Although misclassification generally biases results toward the null, in some instances it can reverse the direction of an association (48–50).

We performed our analyses using a single physical activity estimate obtained at examination 4. Physical activity also was estimated at examinations 11 and 12 that were conducted 14–16 years later. Rank correlations between the physical activity estimated at examination 4 and that at the two later examinations, 0.25 and 0.18, respectively, were low, suggesting that the relative activity levels of the women changed during the follow-up period. Too few breast cancers, however, occurred after these later estimates to examine the relation of more recent physical activity to breast cancer.

In conclusion, our findings do not support a protective effect of moderate-to-heavy physical activity during adulthood for breast cancer but suggest an increased risk among more active women. Because only a few women participated in heavy activities, we cannot make inferences about the relation of more strenuous activity to breast cancer risk. Additionally, our study was limited to adults, and therefore, we could not assess the relation of physical activity at other times of life, such as during adolescence, with breast cancer risk. Future research should address how physical activity at various intensity levels during different stages of life is related to breast cancer risk.

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