Lifetime Recreational and Occupational Physical Activity and Risk of *In situ* and Invasive Breast Cancer

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Abstract

Numerous studies have observed reduced breast cancer risk with increasing levels of physical activity, yet these findings have been inconsistent about optimal times of activity and effect modification by other factors. We investigated the association between recreational and occupational physical activity and breast cancer risk in a population-based case-control study in Massachusetts, New Hampshire, and Wisconsin. During structured telephone interviews, 7,630 controls, 1,689 *in situ*, and 6,391 invasive breast cancer cases, ages 20 to 69 years, reported lifetime history of recreational physical activity and occupation. Neither lifetime recreational nor strenuous occupational physical activity appeared to be associated with risk of breast carcinoma *in situ*. In contrast, recreational physical activity was associated with a reduced risk of invasive breast cancer. After adjustment for potentially confounding factors, women averaging >6 h per week of strenuous recreational activity over their lifetime had a 23% reduction in the odds ratio of invasive breast cancer when compared with women reporting no recreational activity (95% confidence interval, 0.65-0.92; P_{trend} = 0.05). However, this reduction in risk was limited to women without a first-degree family history of breast cancer ($P_{interaction}$ = 0.02). Inverse associations were observed for physical activity early in life, in the postmenopausal years, and in the recent past, but these findings were confined to women without a family history of breast cancer. Lifetime strenuous occupational activity was not associated with invasive breast cancer risk. These results provide further evidence that, for most women, physical activity may reduce the risk of invasive breast cancer. (Cancer Epidemiol Biomarkers Prev 2007;16(2):236–43)

Introduction

Physical activity has received much attention as one of the few modifiable risk factors for breast cancer. Numerous epidemiologic studies have observed a reduced risk of breast cancer with increasing levels of physical activity (1-3). Several biological mechanisms have been proposed to mediate an effect of physical activity on breast cancer risk, including lowering estrogen and growth factor exposures and enhancing immune function (1-3). In 2002, the IARC concluded that ''convincing'' evidence exists for an inverse association between breast cancer risk and physical activity (4).

However, many aspects of the association between physical activity and breast cancer remain unclear. To date, findings have been inconsistent with regard to which times of life are most important for risk reduction and whether the effect of physical activity on breast cancer risk reduction differs in particular subgroups of women (3). The modifying effects of family history of breast cancer (5-7), menopausal status (8), and body mass index (BMI; refs. 5, 9) have yet to be resolved. These issues may have important public health implications and may yield insights into the mechanisms of risk reduction.

Most studies of lifetime physical activity and breast cancer have been limited to either recreational or occupational activity. Few studies have considered both recreational and occupational lifetime physical activity, and even fewer have included household physical activity (10, 11). These limitations may contribute to inconsistencies in the literature about the association of physical activity with breast cancer risk.

Unlike invasive breast cancer, the relationship between physical activity and breast carcinoma *in situ* has not been extensively evaluated. Whereas several studies have presented combined analyses of invasive breast cancer and breast carcinoma *in situ*, few have examined separately the association of physical activity with risk of breast carcinoma *in situ* (12).

The present study investigates the relationship between recreational and strenuous occupational physical activity and breast cancer risk in a population-based case-control study in Wisconsin, Massachusetts, and New Hampshire. The large sample size in this study permitted consideration of whether physical activity has a different influence on the risk of breast carcinoma *in situ* and invasive breast cancer. Information collected on lifetime physical activity was used to evaluate timing of activity in relation to risk and whether inverse associations with physical activity are consistent in subgroups defined by family history of breast cancer, menopausal status, and BMI.

Materials and Methods

This analysis was done with data from the Collaborative Breast Cancer Study, a population-based case-control study conducted in Wisconsin, Massachusetts, and New Hampshire. All interviews were completed between February 1997 and May 2001. The study was conducted according to protocols approved by the institutional review boards at the University of Wisconsin (Madison, WI), Harvard University (Boston, MA), and Dartmouth Medical School (Lebanon, NH).

Selection of Cases. All female residents of Massachusetts (excluding metropolitan Boston), New Hampshire, and Wisconsin, ages 20 to 69 years, with a new diagnosis during 1995 to 2000 of breast carcinoma *in situ* or invasive breast cancer reported to the cancer registry of each state, were eligible for this study. The physician of record for each eligible case subject was contacted by mail to obtain permission to interview the patient. Eligibility was limited to case subjects with listed telephone numbers, driver's licenses verified by self-report (if <65 years of age), and reported dates of diagnosis. The mean time between diagnosis and interview was 17.8 months (range, 4.6-54.5 months) for *in situ* cases and 17.8 months (range, 3.5-55.9 months) for invasive cases.

Of the 2,028 eligible *in situ* cases, physicians refused contact with 49 (2.4%), 11 (0.5%) were deceased, 58 (2.9%) could not be located, and 205 (10.1%) refused to participate. Of the 8,066 eligible invasive cases, physicians refused contact with 147 (1.8%), 302 (3.7%) were deceased, 215 (2.7%) could not be located, and 973 (12.1%) refused to participate. Overall, 1,705 (84%) *in situ* and 6,429 (80%) invasive cases were interviewed. Of those interviewed, 99% of *in situ* cases and 98% of invasive cases were confirmed by histology, cytology, or other means according to the registry reports. Information collected from seven *in situ* cases and eight invasive cases was considered unreliable by the interviewers, leaving a total of 1,698 *in situ* cases and 6,421 invasive breast cancer cases. Of the *in situ* cases, 12.6% were lobular carcinoma *in situ* (International Classification of Diseases for Oncology code 8520/2) and 87.4% were ductal/nonlobular breast carcinoma *in situ*.

Selection of Controls. Controls were randomly selected in each state from the community using two sampling frames: those under 65 years of age were selected from lists of licensed drivers, and those 65 to 69 years of age were selected from a roster of Medicare beneficiaries compiled by the Centers for Medicare and Medicaid Services. Controls were selected at random within 5-year age strata to yield an age distribution similar to the cases enrolled in each state. Controls were required to have no personal history of breast cancer, a listed telephone number, and, if <65 years of age, a self-reported driver's license. Of the 10,161 eligible controls, 78 (0.8%) were deceased, 460 (4.5%) could not be located, and 1,940 (19.1%) refused to participate. Interviews were obtained for 7,683 (76%) of these women, conducted contemporaneously with the case subjects. Information collected from 10 controls was considered unreliable by the interviewers, leaving a total of 7,673 controls for analysis.

Data Collection. Case subjects and controls were sent letters briefly describing the study before they were contacted by telephone by trained interviewers. The 40-min telephone interview elicited information on recreational physical activity, job history, reproductive history, alcohol consumption, height and weight, use of hormones, personal and family medical history, and demographic factors. Information about the woman's personal and family history of cancer was obtained at the end of the interview to maintain blinding. For 95% of *in situ* cases, 91% of invasive cases, and 94% of controls, the interviewers reported being unaware of the woman's case-control status until the end of the interview.

Information on lifetime recreational physical activity and job history was obtained from each subject. As in the Nurses' Health Study (13, 14), we collected information on regular participation in recreational activities, including jogging/ running, bicycling, calisthenics/aerobics/dance, racquet sports, swimming, walking/hiking for exercise, and "other" strenuous individual and team activities. Lifetime history of each recreational activity was assessed with a format of questions originally developed by Bernstein et al. (15), in which subjects reported their age when the activity was started and stopped, the number of months per year, and the number

of hours per week in which it was undertaken. The original Bernstein et al. instrument assessed exercise engaged in for at least 2 h per week at any given age (13) and was later modified to assess exercise engaged in for at least 1 h per week for at least 4 months at any given age (7). In this study, exercise activity for at least 30 min per week for at least 3 months at any given age was included.

Occupational physical activity was ascertained by recording lifetime occupational history. For each job held at least 1 year (beginning at age 14), subjects provided the job title, type of industry, a description of their duties, the year of start and stop, and the number of hours worked per week.

Analysis. For each case, a reference date was defined as the registry-supplied date of breast carcinoma *in situ* or invasive breast cancer diagnosis. For comparability, the control subjects interviewed contemporaneously with cases were assigned an individual reference date. Using the anticipated interview date of the control and a random number based on the normal distribution of days from diagnosis to interview in the cases already interviewed (based on state and 5-year age group relative to the control), the individual control reference date was calculated. This was done to maintain comparability between cases and controls and to maintain interviewer blinding to case-control disease status. Reference age was defined as the woman's age at the reference date. Only exposures that occurred at least a year before the assigned reference date were included in analyses.

To minimize recall bias in the analysis of recreational physical activity, we considered only the six main recreational physical activities mentioned above. Lifetime average number of hours of exercise per week was computed by dividing the total number of hours of exercise between age 14 and a year before the subject's reference date by the number of weeks between these two dates. To consider the intensity of activity, a metabolic equivalent of energy expenditure (MET) value was assigned to each reported activity according to the Compendium of Physical Activities (16). Lifetime average number of MET-hours of exercise per week was computed by multiplying the number of hours of each activity by its MET value, summing these MET-hours, and dividing by the number of weeks between age 14 and a year before the reference date. Recreational activity during specific time intervals (ages 14-22, age 22 to menopause, menopause to 1 year before reference date, and between 11 years and 1 year before reference date) was computed similarly. These times were chosen to be consistent with previous analyses in the literature (12, 17, 18).

Job title was coded according to the U.S. Department of Labor's Dictionary of Occupational Titles (19) nine-digit occupation codes, which are classified into one of five categories of Physical Demands Strength Rating, ranging from sedentary to very heavy. The strength rating reflects the worker's involvement in standing, walking, and sitting as well as the intensity and duration of lifting, carrying, pushing, and pulling (19). Lifetime average number of hours per week of strenuous occupational activity was computed by summing the total number of hours worked in a job with a strength rating of medium, heavy, or very heavy between age 14 and a year before the reference date and dividing by the number of weeks between these two dates. To consider intensity of strenuous occupational activity, MET values of 4 and 6 were assigned to jobs with strength ratings of medium and heavy or very heavy, respectively, to allow calculation of lifetime average MET-hours per week spent in active jobs (similar to ref. 10).

Two measures of total physical activity were created by combining lifetime recreational and occupational activity. First, lifetime average hours of total activity per week was computed by summing a subject's average hours per week of recreational activity and average hours per week spent

working in a job with a strength rating of medium, heavy, or very heavy. Second, lifetime average MET-hours of total activity was computed by summing a subject's lifetime average MET-hours per week of recreational activity with lifetime average MET-hours per week of strenuous occupational activity.

A woman was defined as postmenopausal if she reported a natural menopause (no menstrual periods for at least 6 months) before the reference date. Women who reported taking hormone replacement therapy and still having periods and women who reported hysterectomy alone were classified as (*a*) premenopausal if their reference ages were in the first decile of age at natural menopause among the controls (<41 years of age for current smokers and <43 years of age for nonsmokers), (*b*) postmenopausal if their reference ages were in the highest decile for age at natural menopause in the control group (≥54 years of age for current smokers and ≥56 years of age for nonsmokers) with age at menopause defined as age at hysterectomy or unknown for hormone users still having periods, and (*c*) unknown menopausal status if at intermediate ages (second to ninth decile). Parity was defined as the number of pregnancies lasting at least 6 months. BMI was calculated as weight (kg) at 1 year before the reference date, divided by the tallest adult height $(m)^2$, and categorized according to clinical guidelines (20) as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30 kg/m^2). A woman was considered to have a family history of breast cancer if she reported that her mother, sister, or daughter had been diagnosed with breast cancer.

Multivariable logistic regression models were used to estimate odds ratios (OR), 95% confidence intervals (95% CI) for the OR, and tests for linear trend across ordinal values of categorical variables. Effect modification was evaluated by inclusion of cross-product interaction terms in logistic models. All analyses were done using Statistical Analysis System statistical software version 9 (SAS Institute, Inc., Cary, NC). Exposure categories of physical activity were chosen with equal increments such that the highest category contained approximately the top 5% of active women. ORs were adjusted for potentially confounding variables selected a priori: age at reference date (20-44, 45-49, 50-54, 55-59, 60-64, 65-69 years), state (Wisconsin, Massachusetts, New Hampshire), screening mammograms per year over the last 5 years (0, <1, 1+), family history of breast cancer in mother, sister, or daughter (yes, no), menopausal status (pre, post), parity (0-1, 2, 3, 4+), age at first birth (nulliparous, <20, 20-24, 25-29, 30+), age at menarche (≤11, 12, 13, 14, 15+), age at menopause (<45, 45-49, 50-54, 55+), postmenopausal hormone use (never, former, current), education (<high school, high school graduate, some college, college graduate), alcohol consumption (0, ≤1, 1.1-7, >7 drinks per week), BMI 1 year before the reference date (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2), and weight change since age 18 until 1 year before the reference date (weight loss, gain 0-4.3 kg, gain 4.4-8.6 kg, gain >8.6 kg). For all potentially confounding variables, missing data were categorized as unknown.

Subjects for Analysis. Due to missing information on lifetime recreational physical activity, 43 controls, 9 *in situ* cases, and 30 invasive cases were excluded from all analyses, leaving 7,630 controls, 1,689 *in situ* cases, and 6,391 invasive cases available for analysis. An additional 1,304 controls, 258 *in situ* cases, and 942 invasive cases with incomplete information on lifetime job history were excluded from analyses of occupational and total activity, leaving 6,326 controls, 1,431 *in situ* cases, and 5,449 invasive cases. Women missing occupational physical activity data reported similar levels of recreational physical activity [mean lifetime recreational physical activity (SD), 1.8 (2.9) h per week] as those with complete occupational activity data [mean lifetime recreational physical activity (SD), 1.7 (2.6) h per week]. Excluded women

were similar to participants with regard to family history of breast cancer, age at first birth, parity, and education. However, excluded women tended to be younger, were less likely to report annual mammograms, and were less likely to have used postmenopausal hormones than women with complete job histories.

Reliability Substudy. To assess the reliability of the questionnaire, a sequential sample of breast cancer cases and control women from Wisconsin and New Hampshire was reinterviewed. Approximately 85% of controls, 94% of *in situ* cases, and 88% of invasive cases agreed to be contacted for a second interview. After an average of 3.4 months (range, 1.4-7.9 months), 95% of controls (*n* = 161), 93% of *in situ* cases (*n* = 33), and 98% of invasive cases (*n* = 134) were successfully recontacted and reinterviewed. The Spearman correlation coefficient for the lifetime average hours per week of recreational physical measure was 0.68 (95% CI, 0.58-0.75) for controls, 0.79 (95% CI, 0.53-0.86) for *in situ* cases, and 0.64 (95% CI, 0.50-0.72) for invasive cases. These correlations are comparable with those found by Friedenreich et al. (21) for a similar questionnaire assessing lifetime physical activity.

Results

A comparison of cases and controls by established breast cancer risk factors is shown in Table 1. As expected, women with breast cancer were more likely than controls to have a family history of breast cancer, to be younger at menarche, to be older at first birth and menopause, to have fewer children, and to have used postmenopausal hormones. Furthermore, women with breast cancer, especially those with breast carcinoma *in situ*, had higher utilization of screening mammography. The average age at diagnosis for *in situ* and invasive breast cancer cases was 53.5 years (SD, 8.9 years) and 54.0 years (SD, 9.5 years), respectively. For controls, the average age at the reference date was 53.8 years (SD, 9.6 years).

Breast Carcinoma *In situ*. Lifetime recreational physical activity did not appear to be associated with risk of breast carcinoma *in situ* (Table 2). Weighting recreational activities by level of intensity (MET values) did not significantly affect the results. Similarly, lifetime strenuous occupational activity, as measured by the average number of hours or MET-hours per week in a medium, heavy, or very heavy strength-rated job, was not associated with risk of breast carcinoma *in situ* after adjusting for other risk factors (Table 2). Two measures of total lifetime activity (hours per week and MET-hours per week), which included both recreational and strenuous occupational activity, were also assessed. Although both of these measures suggested a decreased risk of breast carcinoma *in situ* with high total lifetime activity, neither was statistically significant (Table 2).

In analyses of various times of recreational activity, no association was found between risk of breast carcinoma *in situ* and recreational activity between ages 14 and 22, age 22 to age at menopause, age at menopause to 1 year before the reference date, or between 11 years and 1 year before the reference date (data not shown).

The null relation between hours per week of lifetime recreational physical activity and risk of breast carcinoma *in situ* did not appear to be significantly modified by menopausal status (χ^2 = 2.47; degree of freedom (*df*) = 1; $P_{interaction}$ = 0.12), BMI (χ^2 = 4.77; *df* = 3; $P_{interaction}$ = 0.19), or family history of breast cancer (χ^2 = 2.68; *df* = 1; $P_{interaction}$ = 0.10). There was no association between risk of breast carcinoma *in situ* and lifetime recreational physical activity among women with no family history of breast cancer (OR, 0.94; 95% CI, 0.68-1.31; >6 versus 0 h/wk) nor among women with a positive family history of breast cancer (OR, 1.13; 95%

Table 1. Characteristics of breast cancer cases and controls

	Controls (n = 7,630), n (%)*	In situ cases (n = 1,689), n (%)*	Invasive cases (n = 6,391), n (%)*
Reference age (y)			
20-49	2,669 (35.0)	627 (37.1)	2,239 (35.0)
50-59	2,582 (33.8)	599 (35.5)	2,159 (33.8)
60-69	2,379 (31.2)	463 (27.4)	1,993 (31.2)
Menopausal status			
Premenopausal	2,921 (38.3)	714 (42.3)	2,463 (38.5)
Postmenopausal	4,191 (54.9)	847 (50.2)	3,483 (54.5)
Family history of breast cancer			
No	6,438 (84.4)	1,263 (74.8)	4,902 (76.7)
Yes	950 (12.5)	368 (21.8)	1,283 (20.1)
Recent frequency of screening mammograms (per year)[†]			
None	1,131 (14.8)	184 (10.9)	1,060 (16.6)
<1	2,920 (38.3)	452 (26.8)	1,860 (29.1)
≥1	3,451 (45.2)	1,029 (60.9)	3,359 (52.6)
Age at menarche (y)			
≤11	1,513 (19.8)	330 (19.5)	1,363 (21.3)
12	1,755 (23.0)	448 (26.5)	1,547 (24.2)
13	2,091 (27.4)	465 (27.5)	1,767 (27.7)
14	1,189 (15.6)	253 (15.0)	933 (14.6)
≥15	924 (12.1)	161 (9.5)	652 (10.2)
Age at first birth (y)[‡]			
≤19	1,321 (19.8)	223 (15.6)	952 (17.5)
20-24	3,213 (48.2)	650 (45.5)	2,486 (45.6)
25-29	1,504 (22.6)	382 (26.7)	1,374 (25.2)
≥30	606 (9.1)	172 (12.0)	635 (11.7)
Parity			
0	925 (12.2)	250 (14.8)	906 (14.2)
1	821 (10.8)	192 (11.4)	754 (11.8)
2	2,226 (29.2)	558 (33.0)	2,026 (31.7)
3	1,749 (22.9)	395 (23.4)	1,363 (21.3)
≥4	1,871 (24.5)	284 (16.8)	1,309 (20.5)
Age at menopause (y)[§]			
≤44	1,168 (27.9)	218 (25.7)	777 (22.3)
45-49	963 (23.0)	185 (21.8)	778 (22.3)
50-54	1,273 (30.4)	253 (29.9)	1,122 (32.2)
≥55	413 (9.9)	99 (11.7)	408 (11.7)
Postmenopausal hormone use[§]			
Never	2,113 (50.4)	323 (38.1)	1,574 (45.2)
Former	363 (8.7)	78 (9.2)	282 (8.1)
Current	1,669 (39.8)	437 (51.6)	1,580 (45.4)
BMI (kg/m²)			
≤18.5 (underweight)	144 (1.9)	32 (1.9)	87 (1.4)
18.5-24.9 (normal)	3,429 (44.9)	834 (49.4)	2,950 (46.2)
25-29.9 (overweight)	2,425 (31.8)	502 (29.7)	1,980 (31.0)
≥30 (obese)	1,507 (19.8)	299 (17.7)	1,289 (20.2)
Weight change since age 18 (tertiles)			
Weight loss	541 (7.1)	121 (7.2)	401 (6.3)
Gain 0-4.3 kg	2,432 (31.9)	558 (33.0)	2,037 (31.9)
Gain 4.4-8.6 kg	2,154 (28.2)	488 (28.9)	1,859 (29.1)
Gain 8.6 kg	2,194 (28.8)	488 (28.9)	1,956 (30.6)
Typical recent alcohol intake (drinks per week)			
0	1,368 (17.9)	294 (17.4)	1,120 (17.5)
≤1	2,843 (37.3)	620 (36.7)	2,240 (35.1)
1.1-7	2,395 (31.4)	545 (32.3)	2,044 (32.0)
>7	948 (12.4)	216 (12.8)	926 (14.5)
Highest education achieved			
<High school	545 (7.1)	98 (5.8)	386 (6.0)
High school graduate	2,965 (38.9)	620 (36.7)	2,486 (38.9)
Some college	2,036 (26.7)	431 (25.5)	1,642 (25.7)
College graduate	1,993 (26.1)	524 (31.0)	1,801 (28.2)

*Due to missing values, some categories do not sum to 100%.
†Average number of mammograms per year between 6 yr and 1 yr before the reference date.
‡Among parous women only.
§Among postmenopausal women only.

CI, 0.57-2.23; >6 versus 0 h/wk). Similarly, the null relation between strenuous occupational or total activity and risk of breast carcinoma did not appear to be significantly modified by menopausal status, BMI, or family history of breast cancer.

Invasive Breast Cancer. After adjusting for other risk factors, women averaging >6 h per week of recreational physical

activity over their lifetime had a 23% reduction in the risk of invasive breast cancer compared with inactive women (OR, 0.77; 95% CI, 0.65-0.92; Table 3). A borderline significant trend was observed between increasing categories of lifetime recreational activity and risk of invasive breast cancer (P_{trend} = 0.05). A similar inverse association was also observed using MET values to weight recreational activity by intensity of activities (OR, 0.77; 95% CI, 0.65-0.91; >35 versus 0 MET-h/wk; P_{trend} = 0.02). Adjustment for lifetime strenuous occupational activity did not substantially change these estimates (data not shown).

Lifetime strenuous occupational activity did not appear to be associated with invasive breast cancer risk (Table 3). Although both measures of total activity suggested a decreased risk of invasive breast cancer with higher total lifetime activity, neither was statistically significant (Table 3).

In analyses of various times of recreational activity among all women, only activity during the past 10 years was significantly associated with risk of invasive breast cancer (P_{trend} = 0.05; Table 4). Women averaging >6 h per week of recreational physical activity during the past 10 years had a 13% reduction in invasive breast cancer risk (OR, 0.87; 95% CI, 0.77-0.99; >6 versus 0 h/wk).

Family history of breast cancer appeared to modify the relation between risk of invasive breast cancer and lifetime recreational physical activity (χ^2 = 5.86; df = 1; $P_{interaction}$ = 0.02; Table 4). Among women with no family history of breast cancer, women with a lifetime average of >6 h per week of recreational activity had a 27% decreased risk of invasive breast cancer compared with inactive women (OR, 0.73; 95% CI, 0.60-0.88). Lifetime recreational activity was not associated with a reduction in risk among women with a family history of breast cancer (OR, 1.35; 95% CI, 0.82-2.21; >6 versus 0 h/wk). Similarly, family history appeared to modify the association between risk of invasive breast cancer and recreational activity between ages 14 and 22 years and between age 22 and menopause (Table 4). For exercise during these times, reduction in invasive breast cancer risk was limited to women with no family history of breast cancer. Furthermore, the risk reduction associated with recreational physical activity during postmenopausal years and the most recent 10 years was also limited to women with no family history of breast cancer.

The association of recreational physical activity with breast cancer risk did not differ significantly according to menopausal status or BMI, although there was some evidence of interaction by these factors. The reduction in risk associated with lifetime recreational physical activity was stronger for postmenopausal women (OR, 0.74; 95% CI, 0.57-0.95; >6 versus 0 h/wk) than for premenopausal women (OR, 0.87; 95% CI, 0.66-1.15; >6 versus 0 h/wk), but the test for interaction was nonsignificant (χ^2 = 0.36; df = 1; $P_{interaction}$ = 0.55). For BMI, a reduction in risk with greater activity was observed only in nonobese women (OR, 0.73; 95% CI, 0.60-0.89 for women <30 kg/m² versus OR, 1.10; 95% CI, 0.72-1.70 for women ≥30 kg/m², comparing >6 versus 0 h/wk), but again, the test for interaction with BMI did not reach significance (χ^2 = 2.89; df = 3; $P_{interaction}$ = 0.41).

The null relation between lifetime occupational or total activity and invasive breast cancer risk was not significantly modified by family history, menopausal status, or BMI (data not shown).

Discussion

In this study, we observed a reduction in invasive breast cancer risk with increasing recreational physical activity during all times examined. However, this reduction in risk was limited to women with no family history of breast cancer. In contrast, no significant association was observed between risk of breast carcinoma in situ and recreational, occupational, or total physical activity.

Breast Carcinoma *In situ*. A recent study of breast carcinoma *in situ* found a reduction in risk associated with lifetime recreational physical activity, which was limited to women with no family history of breast cancer (12). This reduction in risk was present for all times analyzed (early, recent, and ages 20-34). The study was restricted to women with a screening mammogram within 2 years before their reference date. Using a very similar measure of activity, we were unable to detect an association between breast carcinoma *in situ* and lifetime recreational physical activity and observed no statistically significant modification of this relation by family history. Our study included women regardless of screening history but used statistical adjustment to control for screening frequency. However, even restricting our analysis to women screened annually over the previous 5 years, we still failed to detect an association between lifetime recreational physical activity and breast carcinoma *in situ* (data not shown). Therefore, the reason for these inconsistent results remains unclear. Similarly, we found no evidence of an association between lifetime strenuous occupational physical activity and risk of breast carcinoma *in situ*. To our knowledge, this is the first study evaluating the relation between lifetime occupational activity and breast carcinoma *in situ*.

Invasive Breast Cancer

Recreational Physical Activity. Several studies have examined the relation between lifetime recreational physical activity and breast cancer (5-7, 10, 11, 15, 18, 22). Whereas one of these studies reported no association between lifetime recreational activity and breast cancer risk (11), the remainder have observed risk reductions ranging from 18% to 58%, consistent with our estimate of a 23% reduction in risk for invasive cancer. However, previous studies have generally reported a reduction in risk with ~3 h or ~20 MET-h per week of recreational physical activity, whereas we observed a statistically significant reduction only among women with activity of >6 h or 35 MET-h per week. This finding may be due to our measure of recreational physical activity, which was limited to six main categories of exercise (see Materials and Methods), potentially underestimating total recreational physical activity by exclusion of other activities. However, in analyses that did include "other" activities, we found a similar but attenuated pattern of an inverse association between recreational physical activity and invasive breast cancer risk. This attenuation may possibly be due to recall bias in the open-ended reporting of "other activities" or the inclusion of low-intensity "other" activities.

In women with no family history of breast cancer, we found that recreational physical activity was associated with reduced risk of invasive breast cancer in early, premenopausal, postmenopausal, and recent times (Table 4). The literature has not been consistent as to which life periods are most relevant to the association of physical activity with reduced breast cancer risk. In a previous case-control study, we found that risk of breast cancer was inversely related to strenuous activity between the ages of 14 and 22 years (17). However, two studies of lifetime activity found that risk of breast cancer was reduced with recent or postmenopausal activity but not early activity (18, 22), and a third found no association between either recent or early activity (5). These inconsistent findings could be due to the challenge of measuring past activity or due to

Table 2. ORs and 95% CIs for lifetime physical activity in relation to risk of breast carcinoma *in situ*

Type of strenuous activity	Controls (n = 7,630)	*In situ* cases (n = 1,689)	OR (95% CI)*	OR (95% CI)[†]
Recreational				
0 h/wk	951	188	1.00 (Reference)	1.00 (Reference)
0.1-3 h/wk	5,403	1,210	1.12 (0.94-1.32)	1.01 (0.85-1.21)
3.1-6 h/wk	815	196	1.19 (0.95-1.49)	1.06 (0.84-1.34)
>6 h/wk	461	95	1.03 (0.78-1.35)	0.93 (0.70-1.24)
P for trend			0.54	0.87
0 MET-h/wk	951	188	1.00 (Reference)	1.00 (Reference)
0.1-17.5 MET-h/wk	5,269	1,198	1.13 (0.96-1.34)	1.03 (0.86-1.23)
17.6-35 MET-h/wk	884	200	1.12 (0.89-1.39)	1.00 (0.79-1.26)
>35 MET-h/wk	526	103	0.97 (0.75-1.27)	0.87 (0.66-1.15)
P for trend			0.84	0.32
Occupational				
0 h/wk	3,304	814	1.00 (Reference)	1.00 (Reference)
0.1-12.5 h/wk	1,965	399	0.81 (0.71-0.93)	0.87 (0.76-1.00)
12.6-25 h/wk	648	125	0.77 (0.62-0.95)	0.85 (0.69-1.06)
>25 h/wk	409	93	0.88 (0.69-1.12)	0.93 (0.73-1.19)
P for trend			0.01	0.12
0 MET-h/wk	3,304	814	1.00 (Reference)	1.00 (Reference)
0.1-50 MET-h/wk	1,918	391	0.82 (0.71-0.93)	0.87 (0.76-1.00)
50.1-100 MET-h/wk	640	123	0.77 (0.62-0.94)	0.85 (0.69-1.06)
>100 MET-h/wk	464	103	0.86 (0.69-1.08)	0.93 (0.73-1.17)
P for trend			0.01	0.12
Total activity [‡]				
0 h/wk	381	87	1.00 (Reference)	1.00 (Reference)
0.1-15 h/wk	4,897	1,130	0.98 (0.77-1.25)	0.92 (0.72-1.19)
15.1-30 h/wk	760	151	0.83 (0.62-1.12)	0.83 (0.62-1.13)
>30 h/wk	288	63	0.89 (0.62-1.28)	0.86 (0.59-1.24)
P for trend			0.14	0.22
0 MET-h/wk	381	87	1.00 (Reference)	1.00 (Reference)
0.1-62.5 MET-h/wk	4,766	1,107	0.99 (0.77-1.26)	0.93 (0.72-1.20)
62.6-125 MET-h/wk	826	163	0.83 (0.62-1.10)	0.82 (0.61-1.10)
>125 MET-h/wk	353	74	0.85 (0.60-1.20)	0.82 (0.57-1.17)
P for trend			0.06	0.10

NOTE: Lifetime activity defined as from age 14 to 1 yr before the reference date.
*ORs are adjusted for age and state.
[†]ORs are adjusted for age, state, mammography, menopausal status, family history of breast cancer, parity, age at first birth, age at menarche, age at menopause, postmenopausal hormone use, education, alcohol, BMI, and weight change since age 18.
[‡]Total activity is sum of subject's recreational and occupational activity.

Table 3. ORs and 95% CIs for lifetime physical activity in relation to risk of invasive breast cancer

Type of strenuous activity	Controls (n = 7,630)	Invasive cases (n = 6,391)	OR (95% CI)*	OR (95% CI)[†]
Recreational				
0 h/wk	951	822	1.00 (Reference)	1.00 (Reference)
0.1-3 h/wk	5,403	4,498	0.97 (0.88-1.08)	0.90 (0.81-1.00)
3.1-6 h/wk	815	739	1.06 (0.93-1.22)	0.97 (0.84-1.12)
>6 h/wk	461	332	0.84 (0.71-1.00)	0.77 (0.65-0.92)
P for trend			0.39	0.05
0 MET-h/wk	951	822	1.00 (Reference)	1.00 (Reference)
0.1-17.5 MET-h/wk	5,482	4,586	0.97 (0.88-1.08)	0.91 (0.81-1.01)
17.6-35 MET-h/wk	671	603	1.04 (0.91-1.20)	0.95 (0.83-1.10)
>35 MET-h/wk	526	380	0.85 (0.72-1.00)	0.77 (0.65-0.91)
P for trend			0.27	0.02
Occupational				
0 h/wk	3,304	2,959	1.00 (Reference)	1.00 (Reference)
0.1-12.5 h/wk	1,965	1,595	0.88 (0.81-0.96)	0.93 (0.86-1.02)
12.6-25 h/wk	648	556	0.93 (0.82-1.05)	1.00 (0.88-1.14)
>25 h/wk	409	339	0.88 (0.76-1.03)	0.93 (0.79-1.09)
P for trend			0.02	0.33
0 MET-h/wk	3,304	2,959	1.00 (Reference)	1.00 (Reference)
0.1-50 MET-h/wk	1,918	1,560	0.88 (0.81-0.96)	0.93 (0.86-1.02)
50.1-100 MET-h/wk	640	532	0.90 (0.79-1.02)	0.97 (0.85-1.10)
>100 MET-h/wk	464	398	0.91 (0.79-1.05)	0.97 (0.83-1.12)
P for trend			0.02	0.39
Total activity[‡]				
0 h/wk	381	362	1.00 (Reference)	1.00 (Reference)
0.1-15 h/wk	4,897	4,209	0.90 (0.78-1.05)	0.88 (0.76-1.03)
15.1-30 h/wk	760	639	0.86 (0.72-1.03)	0.87 (0.73-1.05)
>30 h/wk	288	239	0.84 (0.67-1.05)	0.85 (0.67-1.07)
P for trend			0.09	0.22
0 MET-h/wk	381	362	1.00 (Reference)	1.00 (Reference)
0.1-62.5 MET-h/wk	4,766	4,126	0.91 (0.78-1.06)	0.89 (0.76-1.04)
62.5-125 MET-h/wk	826	652	0.81 (0.68-0.97)	0.82 (0.68-0.99)
>125 MET-h/wk	353	309	0.88 (0.71-1.08)	0.88 (0.71-1.09)
P for trend			0.05	0.12

NOTE: Lifetime activity defined as from age 14 to 1 yr before the reference date.
*ORs are adjusted for age and state.
[†]ORs are adjusted for age, state, mammography, menopausal status, family history of breast cancer, parity, age at first birth, age at menarche, age at menopause, postmenopausal hormone use, education, alcohol, BMI, and weight change since age 18.
[‡]Total activity is the sum of subject's recreational and occupational activity.

differing effects of physical activity in population subgroups, particularly with regard to family history of breast cancer.

Previous studies have presented conflicting evidence about effect modification by family history of the relation between physical activity and breast cancer risk. In contrast to our findings, Verloop et al. (5) found that the inverse association between lifetime recreational physical activity and breast cancer risk was stronger in women with a family history of breast cancer, although the interaction was not statistically significant on the multiplicative scale ($P_{interaction}$ = 0.10). At least three studies have found no effect of family history on the relationship between physical activity and breast cancer risk (23-25). However, consistent with our results, three recent studies (6, 7, 12) found that the reduction in breast cancer risk associated with lifetime exercise was limited to women who had no family history of breast cancer. Furthermore, a recent study found that, among carriers of *BRCA* gene mutations, recreational physical activity was not associated with breast cancer risk (26). In our study, family history was observed to modify the association of invasive breast cancer and lifetime recreational physical activity as well as activity during ages 14 and 22 and age 22 and menopause (Table 4). Similarly, the reduction in risk observed with increasing recreational activity during postmenopausal years or the most recent 10-year period was limited to women without a family history of breast cancer. Interestingly, among women with a family history of breast cancer, we found a suggestion of an increased risk of invasive breast cancer with increasing recreational physical activity during ages 14 to 22 and age 22 to menopause. We are unsure of the extent to which chance, selection bias, or reporting bias may be responsible for these results.

Occupational and Total Physical Activity. Whereas fewer studies have examined the relationship between occupational activity and breast cancer risk, the majority have reported an inverse association (1). Very few studies have assessed both lifetime recreational and occupational activity at the same time (5, 10, 11, 18, 27). Verloop et al. (5) found that a combined measure of lifetime occupational and recreational physical activity was associated with a greater reduction in breast cancer risk than recreational activity alone (42% versus 33% risk reduction). Friedenreich et al. (11, 18) created a total lifetime activity measure consisting of recreational, occupational, and household activity, finding that the 30% reduction in breast cancer risk associated with total lifetime activity in postmenopausal women was driven by occupational and household activity. John et al. (10) also combined recreational, occupational, and household activity and found that total activity was associated with a 19% to 25% reduction in breast cancer risk. Whereas each type of activity was separately associated with reduced risk in premenopausal women, only occupational activity was associated with reduced risk in postmenopausal women. In contrast, Yang et al. (27) found that recreational physical activity was more strongly related to breast cancer risk than occupational physical activity, for which a statistically significant relation was not observed. Similarly, in this study, we found that only recreational physical activity was associated with invasive breast cancer risk. Combining recreational and strenuous occupational activity into a total activity measure did not reveal a further risk reduction than recreational activity alone. Furthermore, the null relation between lifetime occupational or total activity and invasive breast cancer risk was not significantly modified

by family history, menopausal status, or BMI. It may be that self-assessed occupational activity level, as used in previous studies (10, 11, 18), provides a more accurate measure of activity than job title–based ratings in which each episode of employment for an individual is assigned the average activity level for that job.

Several limitations should be considered with regard to this study. As with most case-control studies, selection bias and recall bias may have influenced our results. The possibility that healthy, physically active women were more likely to participate cannot be ruled out. The threat of such a selection bias was minimized by excellent participation rates in cases and controls. Moreover, the fact that we observed expected associations between breast cancer risk and established risk factors argues against any strong selection bias in the data. Nevertheless, the direction of such bias is difficult to establish and it is possible that the modest inverse associations observed in this study reflect attenuation due to greater participation of more health conscious and physically active women as cases or, conversely, exaggerated inverse associations due to the preferential enrollment of more active controls.

Although our assessment of the reliability of the recreational physical activity instrument indicated reasonably good reproducibility (see Materials and Methods), the validity of

the instrument has not been assessed. In the assessment of physical activity, recall over long past periods was required. To facilitate recall, participants were prompted to report episodes of specific, vigorous recreational activities (running, swimming laps, etc.). Notably, individual self-reported activity intensity levels were not ascertained. Rather, MET values and Dictionary of Occupational Titles strength ratings typical for each activity were assigned. Given these difficulties in measuring physical activity, nondifferential misclassification would likely bias our results toward the null. However, we cannot exclude the possibility that cases were more (or less) likely to recall strenuous activity than were controls. A further limitation of the study is the omission of household activity. At least one study (11) has found that lifetime household activity was associated with a reduced risk of breast cancer.

Among the strengths of this study are the large sample size, population-based sampling, and the extensive data about potentially confounding variables, including screening mammography. Furthermore, as one of few studies that have measured lifetime recreational and occupational physical activity, we were able to assess the relation of physical activity to breast cancer risk during different times and account for two important sources of physical activity.

Table 4. Recreational physical activity and risk of invasive breast cancer by time of exercise and family history

Period of recreational activity	All women			No family history of breast cancer			Family history of breast cancer		
	Controls (n = 7,630)	Invasive cases (n = 6,391)	OR (95% CI)*	Controls (n = 6,438)	Invasive cases (n = 4,902)	OR (95% CI)*	Controls (n = 950)	Invasive cases (n = 1,283)	OR (95% CI)*
Lifetime[†]									
0 h/wk	951	822	1.00 (Reference)	799	620	1.00 (Reference)	112	155	1.00 (Reference)
0.1-3 h/wk	5,403	4,498	0.90 (0.81-1.00)	4,530	3,435	0.91 (0.81-1.03)	713	931	0.90 (0.69-1.19)
3.1-6 h/wk	815	739	0.97 (0.84-1.12)	705	595	0.99 (0.84-1.16)	88	128	1.01 (0.69-1.49)
>6 h/wk	461	332	0.77 (0.65-0.92)	404	252	0.73 (0.60-0.88)	37	69	1.35 (0.82-2.21)
P for trend			0.05			0.03			0.24
						P for interaction = 0.02[‡]			
Age 14-22[§]									
0 h/wk	3,365	2,871	1.00 (Reference)	2,814	2,205	1.00 (Reference)	448	564	1.00 (Reference)
0.1-3 h/wk	3,021	2,516	0.96 (0.89-1.03)	2,558	1,932	0.94 (0.86-1.02)	377	511	1.03 (0.85-1.25)
3.1-6 h/wk	686	578	0.99 (0.87-1.12)	591	447	0.95 (0.83-1.09)	69	113	1.31 (0.93-1.83)
>6 h/wk	550	425	0.91 (0.79-1.05)	468	317	0.87 (0.74-1.01)	55	95	1.40 (0.97-2.02)
P for trend			0.23			0.05			0.04
						P for interaction = 0.003[‡]			
Age 22-menopause[‖]									
0 h/wk	1,474	1,155	1.00 (Reference)	1,210	863	1.00 (Reference)	229	261	1.00 (Reference)
0.1-3 h/wk	1,832	1,535	0.99 (0.88-1.10)	1,538	1,188	0.97 (0.85-1.10)	248	319	1.10 (0.84-1.45)
3.1-6 h/wk	305	253	0.97 (0.80-1.18)	258	194	0.92 (0.74-1.15)	41	55	1.21 (0.75-1.94)
>6 h/wk	201	138	0.83 (0.65-1.05)	181	99	0.70 (0.53-0.91)	16	35	2.15 (1.11-4.18)
P for trend			0.22			0.03			0.04
						P for interaction = 0.01[‡]			
Postmenopausal[¶]									
0 h/wk	1,213	1,011	1.00 (Reference)	1,013	780	1.00 (Reference)	170	203	1.00 (Reference)
0.1-3 h/wk	1,800	1,416	0.91 (0.81-1.02)	1,489	1,047	0.87 (0.76-0.98)	265	340	1.17 (0.89-1.55)
3.1-6 h/wk	504	424	0.93 (0.79-1.10)	422	336	0.93 (0.78-1.12)	71	83	1.02 (0.68-1.52)
>6 h/wk	292	224	0.86 (0.70-1.05)	259	177	0.80 (0.64-1.00)	29	42	1.25 (0.72-2.18)
P for trend			0.13			0.07			0.50
						P for interaction = 0.68[‡]			
Past 10 yrs**									
0 h/wk	2,063	1,760	1.00 (Reference)	1,730	1,327	1.00 (Reference)	250	349	1.00 (Reference)
0.1-3 h/wk	3,466	2,867	0.92 (0.84-1.00)	2,888	2,189	0.93 (0.85-1.02)	467	595	0.89 (0.72-1.10)
3.1-6 h/wk	1,218	1,064	0.94 (0.84-1.05)	1,045	833	0.94 (0.83-1.06)	147	212	1.00 (0.75-1.33)
>6 h/wk	867	696	0.87 (0.77-0.99)	760	549	0.86 (0.75-0.98)	85	127	1.02 (0.73-1.43)
P for trend			0.05			0.04			0.82
						P for interaction = 0.38[‡]			

*ORs are adjusted for age, state, mammography, menopausal status, family history of breast cancer, parity, age at first birth, age at menarche, age at menopause, postmenopausal hormone use, education, alcohol, BMI, and weight change since age 18.
†Activity from age 14 to 1 yr before the reference date.
‡P for interaction determined by inclusion of cross-product terms in logistic models.
§Women <22 yr are excluded.
‖Postmenopausal women only.
¶Activity from age at menopause to 1 yr before the reference date (includes postmenopausal women only).
**Activity between 11 yrs and 1 yr before the reference date.

Several biological mechanisms have been proposed to explain the reduced risk of breast cancer associated with physical activity. Heavy exercise is associated with delayed menarche, irregular and anovulatory menstrual cycles, and a shortened luteal phase (28-31). Furthermore, postmenopausal women who are physically active have been shown to have lower levels of estrone and estradiol (32-34) as well as increased levels of sex hormone–binding globulin (35). Higher levels of estrogen and lower levels of sex hormone–binding globulin are associated with increased breast cancer risk in postmenopausal women (36). Other potential mechanisms include the prevention of weight gain, regulation of insulin sensitivity, and alterations in immune function (1-3, 35, 37). Bernstein et al. (7) have noted that premenopausal women with a family history of breast cancer tend to have higher estrogen levels compared with control women (38). It may be that the effect of physical activity on lowering estrogen exposure is not sufficient in women with higher estrogen levels.

In summary, this study provides further evidence that recreational physical activity during all periods of life is inversely associated with invasive breast cancer risk. This reduction in invasive breast cancer risk with recreational physical activity was found to be limited to women with no family history of breast cancer. We found no evidence that physical activity is associated with a reduced risk of breast carcinoma *in situ*. Further studies of population subgroups are necessary to gain a better understanding of the relation of physical activity to breast cancer risk and to identify the groups most likely to gain benefit. Future research should examine multiple sources of activity (recreational, occupational, and household) to better assess the true magnitude of the association. Finally, intervention studies assessing the effect of physical activity on estrogen and other hormone exposure and other biomarkers of risk would provide valuable insights on the mechanisms of physical activity in reducing breast cancer risk (39).

Acknowledgments

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