A Prospective Study of Recreational Physical Activity and Breast Cancer Risk

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Background: Increased physical activity has been hypothesized to prevent breast cancer, largely by reducing cumulative lifetime exposure to circulating ovarian hormones. However, epidemiologic findings are inconsistent, and there is no consensus on the best way to quantify physical activity. We thus examined this issue in a large cohort of women, using several different measures of adult physical activity.

Methods: We analyzed data from the Nurses’ Health Study, a prospective study of women aged 30 to 55 years in 1976. In 1980 and on subsequent surveys, women were asked about the average number of hours per week spent in various moderate and vigorous recreational physical activity during the past year. We computed a “baseline-only” (1980) measure of hours per week of physical activity, as well as a cumulative average measure that used updated reports on physical activity. During 16 years of follow-up, we identified 3137 cases of invasive breast cancer (1036 premenopausal and 2101 postmenopausal women). Data were analyzed by use of multivariate pooled logistic regression to produce relative risks of breast cancer, and the associated confidence intervals.

Results: Women who were more physically active in adulthood had a lower risk of breast cancer than those who were less physically active. Comparing those who reported engaging in moderate or vigorous physical activity for 7 or more hours per week with those who engaged in such physical activity for less than 1 hour per week, the relative risk was 0.82 (95% confidence interval, 0.70-0.97), using the cumulative average updating. The dose-response trend was statistically significant ($P = .004$). Using the baseline-only measure of physical activity produced slightly weaker relative risks.

Conclusion: These results contribute to the body of evidence suggesting that higher levels of adult physical activity afford modest protection against breast cancer.

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INCREASED PHYSICAL activity has been hypothesized to prevent breast cancer, largely by reducing cumulative lifetime exposure to circulating ovarian hormones. In some studies, physical activity has been associated with menstrual characteristics, body size, and fat stores, which in postmenopausal women are the locus of conversion of androstenedione to estrogen.

There is currently no scientific consensus on the critical time period of exposure or on the intensity or frequency of physical activity needed to influence breast cancer risk. Consequently, epidemiologic studies of physical activity and breast cancer have been heterogeneous for age at breast cancer diagnosis, the ages at which physical activity is assessed, and methods for measuring intensity, frequency, and duration of physical activity. Such heterogeneity in methods may explain, at least in part, the inconsistency in findings regarding the physical activity–breast cancer relationship. Several studies have reported meaningful reductions in breast cancer risk associated with higher physical activity levels, while others have found modest or no association or even increased risk. However, substantial disagreement still exists even among studies that used comparable methods to measure physical activity at similar points in life.

The strongest reduction in relative risk (RR) was reported by Bernstein et al in a case-control study of women younger than 40 years ($RR = 0.42$ [95% confidence interval (CI), 0.27-0.64] for a lifetime average of 3.8 hours or more of physical activity per week, relative to 0 hours). These researchers used a detailed physical activity assessment instrument to quantify the average number of hours per week of recreational physical activity over the...
SUBJECTS AND METHODS

The Nurses’ Health Study (NHS) is a prospective cohort study established in 1976; 121,701 female registered nurses aged 30 to 55 years were enrolled by responding to a mailed questionnaire about their medical histories and lifestyles. Subsequent questionnaires requesting updated information on risk factors and medical events have been mailed every 2 years. Follow-up in this cohort between 1976 and June 1, 1996, has been 94% of the potential person-years (2,183,490 of 2,313,878 person-years).

ASSESSMENT OF PHYSICAL ACTIVITY

On the 1980 questionnaire, women were first asked about their recreational physical activity patterns. They were asked to report the average number of hours they spent each week during the past year on moderate and vigorous recreational activities including heavy gardening, vigorous sports, jogging, brisk walking or striding, bicycling, heavy housework, etc. On the 1982 questionnaire, women were asked a slightly different question: “For how many hours per week, on average, do you engage in activity strenuous enough to build up a sweat?” In 1986, 1988, 1992, and 1994, women were asked to report the average time spent per week during the past year on specific activities: walking or hiking outdoors, jogging (slower than 10 min/mile), running (10 min/mile or faster), bicycling (including use of a stationary bicycle), lap swimming, playing tennis or squash, and participating in calisthenics, aerobics, aerobic dance, or using a rowing machine. Each woman also reported her usual walking pace: easy (<2 mph), normal (2-2.9 mph), brisk (3-3.9 mph), or very brisk (≥4 mph). For 1980, 1982, 1986, 1988, 1992, and 1994, therefore, we had a measure of average hours per week of moderate or vigorous physical activity. (Walking done at an easy or normal pace was considered light activity, and was not counted in the measure of moderate or vigorous physical activity.) In 1986, 1988, 1992, and 1994, because we had information on specific activities, we were able to create a variable representing average hours per week of vigorous-only physical activity. Vigorous physical activity was defined as any activity with an assigned metabolic equivalent task value21 of 6.0 or greater; in these data, these activities included jogging, running, bicycling, swimming, tennis and/or squash, calisthenics, aerobics, and use of a rowing machine.

We evaluated the association between adult physical activity and breast cancer in several different ways. First, we examined the association between long-term average moderate or vigorous physical activity level and breast cancer risk over the 16-year follow-up period. To represent long-term physical activity levels of individual women as accurately as possible, we created measures of cumulative average adult physical activity level (average number of hours per week) from all available questionnaires up to the start of each 2-year follow-up interval. For example, the incidence of breast cancer from 1980 to 1982 was examined in relation to the physical activity level reported on the 1980 questionnaire; the incidence of breast cancer from 1982 to 1984 was examined in relation to the average physical activity level calculated from the 1980 and 1982 questionnaires; the incidence of breast cancer from 1994 to 1996 was examined in relation to the average physical activity level calculated from the 1980, 1982, 1986, 1988, 1992, and 1994 questionnaires. Since there were no measures of physical activity in 1984 or 1990, the incidence of breast cancer in the 2-year period following these respective years was examined in relation to the average physical activity level calculated from the previous questionnaires. We used the continuous values of hours per week to compute the cumulative averages at each period; we categorized the hours per week into 5 levels after averaging (<1, 1-1.9, 2-3.9, 4-6.9, and ≥7 hours per week). The reference group consisted of women performing less than 1 hour of moderate or vigorous physical activity per week. Second, we examined the association between a single baseline measure of physical activity (1980) and the 16-year risk of breast cancer. Third, we evaluated the effect of vigorous physical activity between 1986 and 1994 on breast cancer risk between 1986 and 1996, using the same cumulative averaging approach described above. When considering vigorous-only physical activity, the reference group consisted of women performing less than 1 hour of moderate or vigorous physical activity per week, while the “exposed” categories pertained to hours per week of vigorous physical activity: 0.1-0.9, 1.0-1.9, 2.0-2.9, 3.0-3.9, and ≥4.0.

DATA ON MENSTRUAL REGULARITY AND BODY SIZE

In 1982, nurses were asked to describe the regularity of their natural menstrual cycles between ages 20 and 35 years, when they were neither pregnant nor taking oral contraceptives. Response categories were very regular, usually regular, usually irregular, and very irregular. For purposes of descriptive reporting, we dichotomized these 4 categories into regular and irregular.

Women reported their current weight and adult height on the initial survey in 1976, and they reported their weight at age 18 years on the 1980 survey. In our analyses, we used body mass index (BMI, calculated as the weight in kilograms divided by the square of the height in meters: weight [kg]/[height (m)]^2) at age 18 years and during the questionnaire years as measures of adiposity. For each 2-year questionnaire cycle, we also calculated the weight change from age 18 years to the current age. The self-reported measure of weight at age 18 years was validated in a subsample of 118 women from a similar cohort through review of college entrance physical examination records. The Spearman correlation between recalled and recorded weight at age 18 years was 0.87. Participants slightly underreported weight at age 18 years (mean difference, 1.4 kg). The precision of self-reported current weight was evaluated in a subsample of 140 participants. Trained technicians visited the substudy participants twice, approximately 6 months apart, to measure weight. The Pearson correlation coefficient between self-reported weight and the average of the technicians’ 2 measurements was 0.97. Participants underreported their current weight; the mean difference was 3.3 kg.

DATA ON OTHER RISK FACTORS

Age at menarche was reported on the baseline questionnaire. Information on other risk factors, including parity,
age at first birth, history of benign breast disease, family history of breast cancer in mother and/or sister, oral contraceptive use, age at menopause, and use of postmenopausal hormones (PMHs), was reported on the baseline questionnaire and was updated every 2 years based on responses to the follow-up questionnaires.

In 1980, 36% of the women were postmenopausal. By the beginning of the last follow-up cycle, in 1994, 85% were postmenopausal (67% of the cases of invasive breast cancer diagnosed during the 16-year follow-up were in postmenopausal women). We examined whether physical activity–breast cancer associations varied by menopausal status, current BMI, weight change between age 18 years and 1980, first-degree family history of breast cancer, parity, history of oral contraceptive use (among premenopausal women), and history of postmenopausal hormone use (among postmenopausal women).

IDENTIFICATION OF INVASIVE BREAST CANCER CASES

On each questionnaire, women were asked if they had been diagnosed with breast cancer in the previous 2 years. Deaths in the cohort were reported by family members and the postal service, or were detected by a search of the National Death Index. For identified cases of breast cancer, we requested permission from each case subject or next of kin to seek hospital records and pathology reports. Pathology reports were obtained for 93% of the cases, and of these, over 99% confirmed the self-reported diagnosis of breast cancer. Those reported cases for which records failed to confirm breast cancer were excluded from analyses, but because the degree of self-reporting accuracy was high, we included the relatively small number of self-reported cases for which records could not be obtained. We excluded in situ cases from analyses.

STATISTICAL ANALYSIS

We used multivariate pooled logistic regression to model the risk of being diagnosed with breast cancer over the 16-year (1980-1996) follow-up period according to the level of cumulative average moderate or vigorous physical activity, as well as according to the level of baseline (1980) moderate or vigorous physical activity. We also modeled the risk of being diagnosed with breast cancer over the 10-year period 1980-1996 according to the average level of vigorous-only physical activity measured from 1986 to 1994.

In each pooled logistic regression model, women were classified by all potential confounders and then by their physical activity level. Each participant contributed person-time of follow-up from the time the initial questionnaire containing the exposure information of interest was returned until the end of follow-up (June 1, 1996), the onset of the outcome of interest, death from any cause, or loss to follow-up. The numbers of cases and person-years that accrued within each exposure level within each stratum were counted. Covariates that remained constant for the duration of the study, such as age at menarche, cases, and person-time of follow-up, were assigned to the unchanging exposure level. For time-varying covariates such as current oral contraceptive use, menopausal status, PMH use, or parity, cases and person-time were reassigned every 2 years according to the updated exposure values reported on each of the biennial questionnaires. (Oral contraceptive use was last asked about in 1986, when most cohort members were aged 45 years and older). From these summary tables, incidence rates were calculated as the sum of the cases divided by the sum of person-time observed for each exposure level. Incidence rate ratios (RRs) for each physical activity level were calculated by dividing the incidence rate in that level by the rate in the reference (lowest physical activity) level. We present both age-adjusted RRs and RRs adjusted simultaneously for a variety of potential confounders.

The covariates of BMI and weight change may act, in part, as intermediate variables through which physical activity influences breast cancer risk. However, in these data, controlling for these 2 covariates singly and in combination with other covariates did not alter RR estimates for any of the physical activity variables. Based on such findings, and to design models that avoid the conceptual problem of including the likely intermediate variables related to weight and weight change, our fully adjusted RRs were adjusted for the following factors: age at baseline (continuous), age at menarche in years (<12, 12, 13, ≥14), parity and age at first birth in years (nulliparous; <1, 1-2 and age at first birth, <25; parity, 1-2 and age at first birth, 25-29; parity, 1-2 and age at first birth, ≥30; parity, ≥3 and age at first birth, <25; parity, ≥3 and age at first birth, ≥25); menopausal status and use of PMHs (premenopausal women; postmenopausal women who never used PMHs; postmenopausal women who used PMHs in the past for less than 5 years; postmenopausal women who used PMHs in the past for 5 years or more; postmenopausal women who currently used PMHs but for less than 5 years; and postmenopausal women who currently used PMHs and had been doing so for 5 or more years); family history of breast cancer in mother and/or sister (yes or no); history of benign breast disease (yes or no); BMI at age 18 years (in quintiles: <19 kg/m², 19-20.4 kg/m², 20.5-21.5 kg/m², 21.6-23.3 kg/m², ≥23.4 kg/m²); and height (≤59 in [≤149.9 cm], 59.1-62 in [150.1-157.5 cm], 62.1-65 in [157.7-165.1 cm], 65.1-68 in [165.4-172.7 cm], >68 in [≥172.7 cm]). All of the above variables with more than 2 categories were controlled as series of dichotomous variables rather than as single (ordinal) variables. For instance, 4 dummy variables were used to code the 5 quintiles of BMI at age 18 years; 5 dummy variables were used to code the 6 parity and age-at-first-birth categories. In addition, models of premenopausal breast cancer included the covariate of oral contraceptive use (never used, used in the past, currently used), while models of postmenopausal breast cancer included the covariate of age at menopause (continuous). We present 2-sided 95% CIs for all RRs.

Only women with nonmissing data on physical activity were included in the analyses. A total of 85 364 women in 1980 served as the initial cohort for all analyses in which 1980 physical activity levels served as baseline. We found 3137 cases of breast cancer among these women over the 16-year follow-up. A total of 77 024 women in 1986 served as the initial cohort for all analyses that begin with 1986 physical activity levels. There were 1221 cases of breast cancer among these women over the 10-year follow-up.
Table 1 gives the crude distribution of relevant covariates according to level of moderate or vigorous physical activity in 1980. Women with higher physical activity levels were younger, and thus more likely to be premenopausal, than those who were less active. They were more likely to have used exogenous hormones. Women who were more active in 1980 were leaner in 1980 than those less active, and were less likely to have put on substantial weight since age 18 years. They were also somewhat leaner at age 18 years. There were few differences in age at menarche, prevalence of nulliparity, history of benign breast disease, first-degree family history of breast cancer, history of cigarette smoking, history of irregular menstrual cycles between ages 20 and 35 years, and height.

Table 2 shows the relationship between the cumulative average measure of hours of moderate or vigorous physical activity during adulthood and breast cancer. Higher levels of moderate or vigorous physical activity were modestly associated with reduced breast cancer risk in this cohort; there was a significant trend in RRs ($P = .004$). Those with an average of 7 or more hours of moderate or vigorous physical activity per week had nearly a 20% lower risk of breast cancer (multivariate-adjusted RR = 0.82 [95% CI, 0.70-0.97]) compared with those reporting less than 1 hour of such physical activity per week. There was little difference between the age-adjusted and multivariate-adjusted RRs. The pattern of RRs was nearly identical in premenopausal and postmenopausal women (data not shown); higher levels of physical activity were modestly inversely associated with breast cancer risk in both groups. The $P$ value for the test of interaction between menopausal status and cumulative average adult physical activity was .09. We also found no variation of the physical activity–breast cancer association across levels of current BMI (in tertiles), weight change between age 18 years and 1980 (in tertiles), first-degree family history of breast cancer, or parity. Among premenopausal women, we found no effect modification by history of oral contraceptive use (never used, used for $<2$ years, used for $\geq 2$ years). Among postmenopausal women, we found no effect modification by history of postmenopausal hormone use (never used, used in the past, currently used).

Table 1. Characteristics of Participants (as Reported up to 1980 Questionnaire) According to Hours per Week of Moderate or Vigorous Activity in 1980* 

<table>
<thead>
<tr>
<th>Activity Level, h/wk</th>
<th>&lt;1.0 (N = 22,209)</th>
<th>1.0-1.9 (N = 7,572)</th>
<th>2.0-3.9 (N = 21,504)</th>
<th>4.0-6.9 (N = 12,618)</th>
<th>$\geq$7.0 (N = 21,461)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, y</td>
<td>48.4 (6.9)</td>
<td>46.5 (7.1)</td>
<td>46.4 (7.2)</td>
<td>47.0 (7.2)</td>
<td>45.4 (7.3)</td>
</tr>
<tr>
<td>Menarche at or before age 14 y</td>
<td>20.2</td>
<td>19.0</td>
<td>19.5</td>
<td>19.5</td>
<td>20.4</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>7.1</td>
<td>7.1</td>
<td>6.4</td>
<td>7.1</td>
<td>7.2</td>
</tr>
<tr>
<td>Ever used oral contraceptives</td>
<td>43.6</td>
<td>49.8</td>
<td>48.3</td>
<td>49.0</td>
<td>54.5</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>44.1</td>
<td>32.4</td>
<td>34.5</td>
<td>37.1</td>
<td>30.4</td>
</tr>
<tr>
<td>Ever used PMHs (among postmenopausal women)</td>
<td>45.6</td>
<td>46.0</td>
<td>45.7</td>
<td>49.7</td>
<td>49.2</td>
</tr>
<tr>
<td>History of benign breast disease</td>
<td>24.0</td>
<td>24.5</td>
<td>23.7</td>
<td>25.2</td>
<td>26.1</td>
</tr>
<tr>
<td>First-degree family history</td>
<td>6.6</td>
<td>6.3</td>
<td>6.0</td>
<td>6.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Never smoked</td>
<td>42.8</td>
<td>44.7</td>
<td>43.0</td>
<td>46.2</td>
<td>43.0</td>
</tr>
<tr>
<td>Irregular menstrual cycles from ages 18-22 y</td>
<td>21.9</td>
<td>22.4</td>
<td>23.2</td>
<td>22.9</td>
<td>22.6</td>
</tr>
<tr>
<td>Irregular menstrual cycles from ages 20-35 y</td>
<td>15.6</td>
<td>14.8</td>
<td>16.2</td>
<td>15.8</td>
<td>14.8</td>
</tr>
<tr>
<td>Mean (SD) BMI at age 18 y, kg/m²</td>
<td>21.4 (3.1)</td>
<td>21.4 (3.1)</td>
<td>21.5 (3.1)</td>
<td>21.4 (2.9)</td>
<td>21.2 (2.8)</td>
</tr>
<tr>
<td>Mean (SD) BMI in 1980, kg/m²</td>
<td>25.1 (5.0)</td>
<td>24.7 (4.7)</td>
<td>24.7 (4.6)</td>
<td>24.4 (4.2)</td>
<td>23.5 (3.8)</td>
</tr>
<tr>
<td>Weight change &gt;10 kg, age 18 y to 1980</td>
<td>40.9</td>
<td>37.6</td>
<td>36.5</td>
<td>34.4</td>
<td>25.8</td>
</tr>
<tr>
<td>Height &gt;170.1 cm (67 in)</td>
<td>10.3</td>
<td>11.0</td>
<td>10.3</td>
<td>11.0</td>
<td>11.1</td>
</tr>
</tbody>
</table>

* Unless otherwise indicated, data are given as a percentage of the total number of participants in the given activity category.
† PMHs indicates postmenopausal hormones; BMI, body mass index.
Table 3 gives the relationship between the 1-time “baseline” (1980) measure of hours of moderate or vigorous physical activity and breast cancer risk. The RRs are attenuated compared with those in Table 2, where a cumulative average measure of physical activity was used. Again, we found no effect modification by any of the covariates listed above. And again, there was little difference between the multivariate-adjusted RRs and those adjusted for age only.

Table 4 gives the relationship between vigorous-only physical activity, measured from 1986 to 1994, and breast cancer risk. The RRs are modestly inverse, and there is not a strong trend with increasing level of vigorous activity. Again, there was little difference between the multivariate-adjusted RRs and those adjusted for age only.

Finally, for comparison with the data in Tables 2 and 3, we ran analyses of moderate or vigorous activity from 1986 onward (data not shown). Since the physical activity questions became more detailed in 1986 and remained the same afterward, we wished to confirm with these questions the patterns noted in Tables 2 and 3, which emerged from data on physical activity levels measured from 1980 onward. Considering a cumulative average measure of moderate or vigorous physical activity from 1986 to 1994 and breast cancer diagnoses between 1986 and 1996, the RRs were nearly identical to those given in Table 2, where physical activity data were updated between 1980 and 1994. Similarly, analysis of a single measure of 1986 moderate or vigorous physical activity level produced RRs very similar to those given in Table 3, where a single measure of physical activity in 1980 was used.

### Table 2. Cumulative Average Hours per Week of Moderate or Vigorous Activity (Updated Every 2 Years, 1980-1994) and Relative Risks (RRs) of Breast Cancer (95% Confidence Intervals [CIs])

<table>
<thead>
<tr>
<th>Activity Level, h/wk</th>
<th>Person-years of Observation (N = 1,193,235)</th>
<th>No. of Cases, 1980-1996 (N = 3137)</th>
<th>Age-Adjusted RR (CI)</th>
<th>Multivariate-Adjusted RR (CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>241,841</td>
<td>736</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0-1.9</td>
<td>231,754</td>
<td>605</td>
<td>0.90 (0.81-1.00)</td>
<td>0.88 (0.79-0.98)</td>
</tr>
<tr>
<td>2.0-3.9</td>
<td>288,099</td>
<td>759</td>
<td>0.91 (0.82-1.00)</td>
<td>0.89 (0.81-0.99)</td>
</tr>
<tr>
<td>4.0-6.9</td>
<td>341,789</td>
<td>860</td>
<td>0.88 (0.80-0.97)</td>
<td>0.85 (0.77-0.94)</td>
</tr>
<tr>
<td>≥7</td>
<td>89,752</td>
<td>177</td>
<td>0.81 (0.69-0.95)</td>
<td>0.82 (0.70-0.97)</td>
</tr>
</tbody>
</table>

* Estimates adjusted for age at baseline, age at menarche, history of benign breast disease, history of breast cancer in mother and/or sister, height, parity and age at first birth, body mass index at age 18 years, menopausal status, and postmenopausal hormone use.
† P = .004 for trend in multivariate-adjusted RRs.

### Table 3. Hours per Week of Moderate or Vigorous Activity (Baseline 1980 Only) and Relative Risks (RRs) of Breast Cancer (95% Confidence Intervals [CIs])

<table>
<thead>
<tr>
<th>Activity Level, h/wk</th>
<th>Person-years of Observation (N = 1,193,235)</th>
<th>No. of Cases, 1980-1996 (N = 3137)</th>
<th>Age-Adjusted RR (CI)</th>
<th>Multivariate-Adjusted RR (CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>301,323</td>
<td>872</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0-1.9</td>
<td>106,749</td>
<td>302</td>
<td>1.03 (0.90-1.17)</td>
<td>1.03 (0.90-1.17)</td>
</tr>
<tr>
<td>2.0-3.9</td>
<td>302,530</td>
<td>791</td>
<td>0.97 (0.88-1.07)</td>
<td>0.97 (0.88-1.07)</td>
</tr>
<tr>
<td>4.0-6.9</td>
<td>177,071</td>
<td>448</td>
<td>0.93 (0.83-1.04)</td>
<td>0.90 (0.80-1.01)</td>
</tr>
<tr>
<td>≥7</td>
<td>305,562</td>
<td>724</td>
<td>0.91 (0.82-1.00)</td>
<td>0.89 (0.80-0.98)</td>
</tr>
</tbody>
</table>

* Estimates adjusted for age at baseline, age at menarche, history of benign breast disease, history of breast cancer in mother and/or sister, height, parity and age at first birth, body mass index at age 18 years, menopausal status, and postmenopausal hormone use.
† P = .004 for trend in multivariate-adjusted RRs.

### Table 4. Cumulative Average Hours per Week of Vigorous Activity (1986-1994) and Relative Risks (RRs) of Breast Cancer (95% Confidence Intervals [CIs])

<table>
<thead>
<tr>
<th>Activity Level, h/wk</th>
<th>Person-years of Observation (N = 384,541)</th>
<th>No. of Cases, 1986-1996 (N = 11,225)</th>
<th>Age-Adjusted RR (CI)</th>
<th>Multivariate-Adjusted RR (CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 (any activity)</td>
<td>159,986</td>
<td>433</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0-1.9 (vigorous)</td>
<td>114,713</td>
<td>170</td>
<td>0.98 (0.86-1.12)</td>
<td>0.95 (0.83-1.09)</td>
</tr>
<tr>
<td>2.0-3.9 (vigorous)</td>
<td>47,334</td>
<td>128</td>
<td>0.89 (0.73-1.06)</td>
<td>0.85 (0.71-1.03)</td>
</tr>
<tr>
<td>4.0-6.9 (vigorous)</td>
<td>22,455</td>
<td>56</td>
<td>0.89 (0.70-1.15)</td>
<td>0.90 (0.70-1.16)</td>
</tr>
<tr>
<td>≥7 (vigorous)</td>
<td>40,053</td>
<td>37</td>
<td>0.87 (0.72-1.06)</td>
<td>0.87 (0.71-1.06)</td>
</tr>
</tbody>
</table>

* Estimates adjusted for age at baseline, age at menarche, history of benign breast disease, history of breast cancer in mother and/or sister, height, parity and age at first birth, body mass index at age 18 years, menopausal status, and postmenopausal hormone use.
†† P = .11 for trend in multivariate-adjusted RRs.

Table 2 gives the relationship between the 1-time “baseline” (1980) measure of hours of moderate or vigorous physical activity and breast cancer risk. The RRs are attenuated compared with those in Table 2, where a cumulative average measure of physical activity was used. Again, we found no effect modification by any of the covariates listed above. And again, there was little difference between the multivariate-adjusted RRs and those adjusted for age only.

### Table 3

Table 3 gives the relationship between the 1-time “baseline” (1980) measure of hours of moderate or vigorous physical activity and breast cancer risk. The RRs are attenuated compared with those in Table 2, where a cumulative average measure of physical activity was used. Again, we found no effect modification by any of the covariates listed above. And again, there was little difference between the multivariate-adjusted RRs and those adjusted for age only.

### Table 4

Table 4 gives the relationship between vigorous-only physical activity, measured from 1986 to 1994, and breast cancer risk. The RRs are modestly inverse, and there is not a strong trend with increasing level of vigorous activity. Again, there was little difference between the multivariate-adjusted RRs and those adjusted for age only, and there was a similar pattern of RRs across strata of menopausal status, current BMI, weight change, first-degree family history of breast cancer, parity, history of oral contraceptive use (among premenopausal women), and history of PMH use (among postmenopausal women).

Finally, for comparison with the data in Tables 2 and 3, we ran analyses of moderate or vigorous activity from 1986 onward (data not shown). Since the physical activity questions became more detailed in 1986 and remained the same afterward, we wished to confirm with these questions the patterns noted in Tables 2 and 3, which emerged from data on physical activity levels measured from 1980 onward. Considering a cumulative average measure of moderate or vigorous physical activity from 1986 to 1994 and breast cancer diagnoses between 1986 and 1996, the RRs were nearly identical to those given in Table 2, where physical activity data were updated between 1980 and 1994. Similarly, analysis of a single measure of 1986 moderate or vigorous physical activity level produced RRs very similar to those given in Table 3, where a single measure of physical activity in 1980 was used.

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In this large prospective study, we found evidence of a modest inverse association between higher moderate or vigorous physical activity levels and breast cancer risk, especially when a cumulative average measure of activity was used. Relative risks were attenuated when we considered a single baseline measure of physical activity. Results for vigorous-only physical activity were also modest. In all cases, age-adjusted RRs were changed little by adjustment for a variety of covariates. Unlike Bernstein et al9 and Thune et al,12 we found no evidence that any physical activity-breast cancer associations varied across subgroups of women.

Bernstein et al9 have argued that lifetime physical activity is the critical variable affecting breast cancer risk. If correct, this hypothesis may explain in part why we observed stronger inverse associations when we used a cumulative average measure of physical activity than when we considered a single baseline measure only. Women who were in the higher physical activity levels under a cumulative averaging approach must have been consistently highly active, while for women in the higher physical activity levels on the single 1980 measure, this was not necessarily so. In other words, use of a single point-in-time measure of physical activity is more likely than a repeated measure to result in misclassification of women with regard to a "regular" physical activity level. Such misclassification, which is likely nondifferential by disease status in a prospective study, would result in attenuated RRs. Obviously, however, none of our measures could be taken as reflective of lifelong average physical activity, and even our cumulative 16-year averaging does not represent a "lifetime" average. It is possible that misclassification (with regard to lifetime average) introduced by our 16-year follow-up measure may have attenuated an even stronger inverse relationship.

It is important to recognize, however, that the hypothesis of Bernstein et al9 regarding lifetime physical activity is not consistently supported in the physical activity-breast cancer literature. Other studies in which inverse associations were observed, such as that of Thune et al12 used physical activity assessment methods that were less detailed than ours and covered shorter periods of time. To our knowledge, there is currently no consensus regarding the critical period in which to measure the effect of physical activity on breast cancer risk. If physical activity at different times in life (relative to the time of breast cancer diagnosis) exerts different effects on breast cancer risk, our method of cumulative averaging of physical activity level may group together women of heterogeneous risks, since our data indicate substantial fluctuation in physical activity levels over time. Such fluctuation means that women with the same cumulative average physical activity level may have had very different patterns of physical activity over time.

We found no evidence in these data that vigorous physical activity (at least as measured over a 10-year follow-up period) is more likely to reduce breast cancer risk than less strenuous activity; women in the highest category of vigorous activity (>4 hours per week) had only a 10% to 15% lower risk of breast cancer than women in the reference category (<1 hour of moderate or vigorous activity per week). The most popular activity overall among women in this cohort was walking; on average, 40% of all hours of moderate or vigorous activity in this cohort were devoted to walking. (The most common vigorous activities were bicycling and participating in aerobics.) Studies of other disease outcomes in this cohort have similarly found that physical activity comprised mainly of walking is as effective as more strenuous activity in reducing disease risk.24,25

We have good evidence that our measures of physical activity are informative with regard to specified periods. The measures are associated as expected with current BMI and weight gain. In a validation study of the instrument used to assess recent physical activity in a similar cohort of women,26 the Pearson correlation coefficient between physical activity reported in 7-day diaries (mailed out at intervals of 3 months over the course of a year) and the questions used on the survey was relatively high (0.62). This physical activity assessment instrument has been shown to be predictive of several disease outcomes, including type 2 diabetes mellitus in women,27 colon cancer in men and women,25,28 gallstones in men,29 and coronary heart disease and stroke in women.30

In a recently published study conducted among the younger NHS II cohort,10 we found no association between recent moderate or vigorous physical activity, measured with the same instrument described in this report, and premenopausal breast cancer risk; all reported RRs were 1.0. In these NHS II analyses, however, there were only 6 years of follow-up compared with the 16 years of follow-up reported herein. Further, premenopausal women in the NHS II cohort were on average 8 to 10 years younger than those described herein. The association between physical activity and breast cancer may be hypothesized to be closer to the null among young women, because among such women a relatively large proportion of breast cancer may be attributable to highly penetrant genetic mutations, and thus may be less amenable to primary prevention through means such as high physical activity levels. Second, there is evidence that among young women, adiposity offers protection from breast cancer. Therefore, physical activity, which tends to decrease adiposity, may not lead to an average reduction in risk. As women approach the perimenopausal state, adipose tissue becomes a more important source of circulating estrogens7,8 and the relationship between adiposity and breast cancer risk becomes positive.31,32 In women in this age range, we would expect that physical activity would be more likely to decrease average breast cancer risk, partly through its effect on adiposity.

In summary, these results contribute to the body of evidence suggesting that higher levels of physical activity convey modest protection against breast cancer. As noted by a recent review of this topic,33 because of the heterogeneity of measurement methods, the disagreements in study findings, and the lack of a clear biological hypothesis underpinning the physical activity-breast cancer relationship, future epidemiologic studies should focus on improving assessment of lifetime physical activity from all sources. Such methodologic improve-
ments will be necessary if epidemiologists are to clarify whether there is a meaningful dose-response relationship or, to reduce lifetime breast cancer risk, an optimal period, duration, frequency, or intensity of physical activity. In the meantime, however, there is a large body of consistent epidemiologic evidence showing that women with higher physical activity levels are at reduced risk of many relatively common diseases and disabilities, including coronary heart disease, stroke, colorectal cancer, type 2 diabetes mellitus, and osteoporotic fractures. All women thus should be encouraged to engage in regular physical activity as part of a lifestyle to maintain good health.

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