Physical Activity and Breast Cancer Risk in Women Aged 20–54 Years

Janneke Verloop, Matti A. Rookus, Karin van der Kooy, Flora E. van Leeuwen

Background/Methods: Although several studies have suggested that physical activity is associated with a decreased risk of breast cancer, such a decrease has not been found consistently, perhaps because physical activity was assessed in different ways and for restricted periods. Few studies have assessed the risk of breast cancer in relation to lifetime physical activity. We used data from a population-based, case–control study, including 918 case subjects (aged 20–54 years) and 918 age-matched population control subjects, to examine associations between breast cancer risk and physical activity at ages 10–12 years and 13–15 years, lifetime recreational activity, and title of longest held job. Results: Women who were more active than their peers at ages 10–12 years had a lower risk of breast cancer (odds ratio [OR] = 0.68; 95% confidence interval [CI] = 0.49–0.94). Women who had ever engaged in recreational physical activity had a reduced risk of breast cancer compared with inactive women (OR = 0.70; 95% CI = 0.56–0.98). Neither very early recreational activity (before age 20 years) nor recent activity (last 5 years) was associated with a greater reduction in risk than recreational activity in the intermediate period. Furthermore, women who started recreational activities after age 20 years and women who started earlier and continued their activities throughout adult life experienced a similar reduction in risk. Lean women, i.e., women with a body mass index (weight in kg/height in m²) less than 21.8 kg/m², appeared to have a lower risk associated with recreational physical activity than women with a body mass index greater than 24.5 kg/m² (OR = 0.57 [95% CI = 0.40–0.82] and OR = 0.92 [95% CI = 0.65–1.29], respectively). Conclusions: Our findings support the hypothesis that recreational physical activity is associated with a decreased risk of breast cancer. Physical activity in early or recent life does not appear to be associated with additional beneficial effects. [J Natl Cancer Inst 2000;92:128–35]

Since Frisch et al. (1) reported a decreased risk of breast cancer in former college athletes in 1985, many studies [reviewed in (2,3)] have examined the role of physical activity in breast cancer etiology. Several biologic mechanisms have been suggested, including effects on endogenous hormone metabolism, body mass, energy balance, and immunity. Although the results from cohort studies seem to be less consistent than those from case–control studies, the majority of studies appear to suggest a protective role for physical activity. However, the extent of the decrease in risk has varied considerably across studies. A trend of decreased risk associated with higher levels of physical activity has been found in many studies (1,4–18) but not in all studies (19–26). Some studies (9,12,14,16) have suggested that, in certain subgroups of women (e.g., lean or parous women), physical activity appears to be associated with a greater decrease in risk of breast cancer.

The measurement of physical activity is a complicated issue, and inconsistent study results may be partly related to differences in the ways the studies assessed physical activity. So far, information on both leisure time and occupational activities has been collected in six studies (5,12,14,17,18,22). Only one follow-up study (22) has assessed physical activity from all sources, including activities of daily living. Most studies collected information on physical activity within a restricted period. To date, to our knowledge, only one case–control study (9) has reported on lifetime recreational activity.

We examined the association between physical activity and the risk of breast cancer in a population-based, case–control study in The Netherlands. We focused on the assessment of lifetime recreational physical activity. In addition, we examined the effects of physical activity before age 20 years because, in this period of the onset of menses and breast development, physical activity might have a stronger protective effect (27). We also collected information on occupational activity.

SUBJECTS AND METHODS

This population-based, case–control study was conducted to investigate the relationship between oral contraceptive use and the risk of breast cancer. The design of the study was described in detail elsewhere (28). Briefly, 918 case subjects (aged 20–54 years) diagnosed with invasive breast cancer from 1986 through 1989 were included in the study. They resided in one of four regions covered by population-based regional cancer registries in The Netherlands. In the two western regions (Amsterdam and West), the case subjects were younger than 45 years of age; in the two southeastern regions (East and Eindhoven), they were younger than 55 years of age. Each patient was pair-matched by age (within 1 year) and region with a control subject (for a total of 918 control subjects), who was randomly selected from municipal registries that fully cover the Dutch population. The response rates of case subjects and of control subjects were 60% and 72%, respectively. A nonresponse study among case subjects (28) suggested that the majority of nonresponders had not been informed about the study by their physicians. A nonresponse study among control subjects (28) showed that responders tended to have a more healthy lifestyle (i.e., less smoking and less alcohol consumption) than nonresponders. Physical activity among nonresponding control subjects was not assessed.

Assessment of Physical Activity

Information on physical activity and other risk factors was collected by trained interviewers during an interview in the subject’s home. Both members of a matched pair were interviewed by the same interviewer. The interview was structured by a questionnaire and a calendar on which all major life events were indicated. Each control subject was assigned a date of pseudodiagnosis, which is the date on which she was exactly as old as her matched case subject at diagnosis. The analysis was restricted to events that had occurred in the period before

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For each subject, we obtained information on lifetime recreational physical activity and job history. First, study subjects were asked to compare their total physical activity at the ages 10–12 years and 13–15 years with the activity of their peers. Possible answers were less active, equally active, or more active.

Second, lifetime recreational activity was assessed by asking the subjects whether they had been engaged in vigorous physical activity for at least 6 months (an episode) when they were 10 years old and whether this pattern had changed when they grew older. For each reported episode, we asked for the type of activity, starting and stopping dates, and frequency. Frequency was measured as the number of times per week. Twenty-two percent of the women reported nonrecreational activities, such as household actions, health care, farm or agricultural work, and cleaning work. Comparison of these reported activities with the reported longest held occupation (see below) revealed that there was a partial overlap, suggesting that the report of vigorous nonrecreational activity was rather subjective. Given these limitations, we restricted the analysis to recreational activities. Total duration of recreational activities in years was calculated by summing up the durations of all episodes (accounting for overlap). The mean frequency of activities within episodes of physical activity was calculated as the average frequency, weighted by the duration of the episode for each activity (years).

For each type of activity, a metabolic equivalent (MET) score was assigned, as described by Ainsworth et al. (29), a method that was also used in other studies (11,13,16,24). An MET score is defined as the ratio of the associated metabolic rate for the specific activity divided by the resting metabolic rate. A total MET score was calculated for the various activities, weighted by the duration (in years) of each activity. For example, being active for 3 years in gymnastics (MET score of 4) and being active for 2 years in competitive basketball (MET score of 8) gives a weighted MET score of 

\[
(4 \times 3) + (8 \times 2)/5 = 5.6
\]

Finally, information about occupation was collected by asking for the job title in which the subject had worked for the longest period during life. Each job title was categorized independently by two of us (J. Verloop and M. A. Rookus) into one of the following three categories of physical activity during work: 1) more than 80% sedentary activity during work (light), 2) 20–80% sedentary activity (moderate), and 3) less than 20% sedentary activity (vigorous). This classification is comparable with that of other studies (8,21). The discrepancy between the two researchers who performed the classification was less than 5%. Consensus was obtained by mutual discussions. Because of the small numbers in the third category, the second and third categories were combined in the analysis.

Data on Other Risk Factors

In addition, we obtained complete information on reproductive and contraceptive histories, family history of breast cancer, BMI (calculated from self-reported weight and height [kg/m²] at (pseudo)diagnosis, lifetime smoking habits, lifetime alcohol consumption, premenstrual complaints (i.e., regularly suffering from a headache, tiredness, pain of the breasts, back pain, or abdominal pain), and menstrual complaints (i.e., regularly having abdominal cramps, dizzi-ness, pain in the back, headache, or severe bleeding).

Statistical Analysis

Differences between group means and categories were tested by Student’s t test and Pearson’s χ² test, respectively. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by multivariable conditional logistic regression methods for individually matched case–control studies (30). Forward step-wise confounder selection, in which the effect of adding one confounder at a time is evaluated, was based on a more than 10% change in the risk estimate of the exposure variable of interest. Crude ORs were presented when the ORs adjusted for all selected confounders differed by less than 10% from the crude estimates. Stratified analyses were done for education, BMI age at menarche, family history of breast cancer, benign breast disease, parity, duration of breast feeding, smoking, and alcohol consumption. The presence of an interaction was assessed by testing the product terms in both a multiplicative model and an additive risk model (31). All P values assessing interaction terms are two-sided.

RESULTS

The distribution of potential confounders according to recreational and occupational activities among control subjects is summarized in Table 1. Compared with inactive women, women who reported ever engaging in recreational physical activity were younger, better educated, and more likely to have a family history of breast cancer, to be nulliparous, to have a lower BMI, and to smoke. They did not differ from inactive women with respect to a history of benign breast disease, age at menarche, at first full-term pregnancy, duration of breast feeding, (pre) menstrual complaints, and alcohol consumption. Women who were engaged in work that was mainly sedentary were younger, were better educated, were more often nulliparous, had a later age at first full-term pregnancy, had fewer premenopausal complaints, and had a slightly lower BMI. No differences were seen for other risk factors. The majority of case subjects and control subjects were premenopausal (89.0% and 89.5%, respectively; data not shown).

In this study, we assessed total physical activity, including recreational and nonrecreational activities, at the age of 10–15 years compared with peers (Table 2). Women who reported being more active than their peers at ages 10–12 years had a 32% reduction in the risk of breast cancer (OR = 0.68; 95% CI = 0.49–0.94). However, women who were more active than their peers at ages 10–12 years and at ages 13–15 years had no further reduction in the risk of breast cancer (OR = 0.72; 95% CI = 0.50–1.03; data not shown).

Analyses of lifetime recreational physical activity (Table 3) showed that active women had a 30% reduction in the risk of breast cancer compared with women who had never engaged in recreational activities (OR = 0.70; 95% CI = 0.56–0.88). Adjustment for confounders (Table 3) and additional adjustment for occupational activity did not change the OR (data not shown). For women whose occupation involved less than or equal to 80% sedentary activities, a small reduction in the risk of breast cancer was observed (OR = 0.92; 95% CI = 0.75–1.11). Adjustment for confounders (Table 3) and recreational activity did not change this risk estimate (data not shown). Classification of women according to both recreational and occupational physical activities revealed a 39% reduction in the risk of breast cancer for women who were engaged in both activities, compared with inactive women (OR = 0.61; 95% CI = 0.44–0.85). We further evaluated the risk of breast cancer in relation to recreational physical activity by examining the effects of lifetime duration (years) and the effects of mean frequency and mean intensity within periods of physical activity. The reported activities had MET scores that varied between 3.0 and 10.0. For each of the three components (i.e., duration, frequency, and intensity), a 30% reduction in risk was already associated with the lowest level of physical activity. No further decrease in risk was found for higher levels of physical activity. Furthermore, the ORs for each of the three components were not materially altered by adjustment for the others. When recreational activity was classified according to a combination of duration, frequency, and intensity of activities, the physical activity of women in the highest tertiles of each of the three components (extremely active) was associated with a 42% reduction in the risk of breast cancer (OR = 0.58; 95% CI = 0.38–0.90).

Stratification according to various risk factors for breast cancer (Table 4) showed that the association with physical activity appeared to be stronger in women with a family history of breast cancer than in women without such a family history. The interaction was highly statistically significant on an additive scale (P_interaction = .001) but did not reach statistical significance on
a multiplicative scale \((P_{\text{interaction}} = .10)\). When we stratified the data according to BMI, we found that the reduction in risk of breast cancer associated with recreational activities was greater for women with a BMI of less than 21.8 kg/m\(^2\) than for women with a BMI of more than 24.5 kg/m\(^2\) (OR = 0.57 [95% CI = 0.40–0.82] versus OR = 0.92 [95% CI = 0.65–1.29], respectively), although the test for neither additive nor multiplicative interaction was statistically significant \((P = .12\) and \(P = .13\), respectively). In women with a history of benign breast disease, physical activity was associated with an increased risk of breast cancer, whereas in active women without such a history, physical activity was associated with a reduced risk (test interaction: \(P = .10\) [additive] and \(P = .02\) [multiplicative]). Furthermore, the protective effect of physical activity appeared to be slightly stronger among nulliparous women (test interaction: \(P = .06\) [additive] and \(P = .14\) [multiplicative]). No interaction with other risk factors was found, and no interaction between these risk factors and occupational activity was found.

When we examined physical activity in three different time windows—i.e., 1) before age 20 years, 2) from age 20 years to 5 years before (pseudo)diagnosis, and 3) from 5 years before (pseudo)diagnosis to (pseudo)diagnosis—we found rather similar risk reductions for each window separately (Table 5). We found a statistically nonsignificant reduction for the first and
Table 2. Physical activity at ages 10–12 years and 13–15 years and risk of breast cancer

<table>
<thead>
<tr>
<th>Activity compared with that of peer group at age 10–12 y</th>
<th>No. of case subjects (%)</th>
<th>No. of control subjects (%)</th>
<th>Univariate OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less active</td>
<td>122 (13.3)</td>
<td>96 (10.5)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>Equally active</td>
<td>577 (62.9)</td>
<td>567 (61.8)</td>
<td>0.82 (0.61–1.09)</td>
</tr>
<tr>
<td>More active</td>
<td>211 (23.0)</td>
<td>247 (26.9)</td>
<td>0.68 (0.49–0.94)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (0.9)</td>
<td>8 (0.9)</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity compared with that of peer group at age 13–15 y</th>
<th>No. of case subjects (%)</th>
<th>No. of control subjects (%)</th>
<th>Univariate OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less active</td>
<td>125 (13.6)</td>
<td>101 (11.0)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>Equally active</td>
<td>537 (58.5)</td>
<td>544 (59.3)</td>
<td>0.81 (0.61–1.07)</td>
</tr>
<tr>
<td>More active</td>
<td>248 (27.0)</td>
<td>263 (28.6)</td>
<td>0.77 (0.57–1.05)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (0.9)</td>
<td>10 (1.1)</td>
<td>—</td>
</tr>
</tbody>
</table>

*OR = odds ratio; CI = confidence interval. Adjustment for confounding did not change the ORs.

Table 3. Lifetime physical activity and the risk of breast cancer

<table>
<thead>
<tr>
<th>Lifetime recreational activities</th>
<th>No. of case subjects (%)</th>
<th>No. of control subjects (%)</th>
<th>Univariate OR (95% CI)*</th>
<th>Multivariate OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>443 (48.3)</td>
<td>386 (42.0)</td>
<td>1.00 (referent)</td>
<td>1.01† (referent)</td>
</tr>
<tr>
<td>Yes</td>
<td>475 (51.7)</td>
<td>532 (58.0)</td>
<td>0.70 (0.56–0.88)</td>
<td>0.67 (0.53–0.84)</td>
</tr>
<tr>
<td><strong>Lifetime duration of recreational activities, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5–5.0</td>
<td>122 (13.3)</td>
<td>151 (16.4)</td>
<td>0.64 (0.48–0.87)</td>
<td>0.63 (0.46–0.85)‡</td>
</tr>
<tr>
<td>5.1–9.0</td>
<td>115 (12.5)</td>
<td>120 (13.1)</td>
<td>0.75 (0.54–1.05)</td>
<td>0.74 (0.54–1.03)</td>
</tr>
<tr>
<td>9.1–16.0</td>
<td>127 (13.8)</td>
<td>133 (14.5)</td>
<td>0.76 (0.56–1.02)</td>
<td>0.75 (0.55–1.02)</td>
</tr>
<tr>
<td>&gt;16</td>
<td>111 (12.1)</td>
<td>128 (13.9)</td>
<td>0.68 (0.49–0.93)</td>
<td>0.67 (0.48–0.93)</td>
</tr>
<tr>
<td><strong>Mean frequency of recreational activities, No. of times/wk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>115 (12.5)</td>
<td>139 (15.1)</td>
<td>0.63 (0.46–0.86)</td>
<td>0.62 (0.45–0.85)‡</td>
</tr>
<tr>
<td>1.1–1.8</td>
<td>96 (10.5)</td>
<td>127 (13.8)</td>
<td>0.57 (0.41–0.79)</td>
<td>0.54 (0.38–0.77)</td>
</tr>
<tr>
<td>1.9–2.6</td>
<td>126 (13.7)</td>
<td>132 (14.4)</td>
<td>0.74 (0.55–1.01)</td>
<td>0.71 (0.52–0.97)</td>
</tr>
<tr>
<td>&gt;2.6</td>
<td>138 (15.0)</td>
<td>134 (14.6)</td>
<td>0.81 (0.61–1.01)</td>
<td>0.84 (0.62–1.13)</td>
</tr>
<tr>
<td><strong>Mean intensity of recreational activities, mean MET score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.0–4.2</td>
<td>110 (12.0)</td>
<td>131 (14.3)</td>
<td>0.67 (0.49–0.92)</td>
<td>0.66 (0.48–0.90)‡</td>
</tr>
<tr>
<td>4.3–5.3</td>
<td>95 (10.3)</td>
<td>130 (14.2)</td>
<td>0.57 (0.41–0.79)</td>
<td>0.56 (0.40–0.78)</td>
</tr>
<tr>
<td>5.4–6.3</td>
<td>148 (16.1)</td>
<td>133 (14.5)</td>
<td>0.86 (0.64–1.15)</td>
<td>0.85 (0.63–1.14)</td>
</tr>
<tr>
<td>&gt;6.3</td>
<td>122 (13.3)</td>
<td>138 (15.0)</td>
<td>0.69 (0.51–0.94)</td>
<td>0.69 (0.50–0.94)</td>
</tr>
</tbody>
</table>

*OR = odds ratio; CI = confidence interval.
†ORs are adjusted for family history of breast cancer.
‡ORs are adjusted for family history of breast cancer, education, and smoking.
§ORs are adjusted for family history of breast cancer, education, smoking, occupational activity, and the other recreational physical activity variables.
¶MET = metabolic equivalent.
#ORs are adjusted for education.
**Extreme activities = highest tertiles of frequency (more than two times/wk), duration (>11 years), and intensity (>5.5 MET score). Moderate activities = all recreational activity other than extreme activities.
Our results support the hypothesis that physical activity protects premenopausal women against breast cancer. For women who had ever been engaged in recreational physical activity compared with inactive women, physical activity was associated with a 30% reduction in their risk of breast cancer. No further risk decrease was associated with a long duration of physical activity or a high frequency or intensity of activity during active periods. We could not distinguish a specific period in life in which the decrease in risk associated with physical activity was most pronounced. Several strong and weak points in our study should be considered in the interpretation of these results.

All studies of physical activity and the risk of breast cancer suffer to a greater or lesser extent from misclassification bias. Measuring physical activity in epidemiologic studies is difficult, and different methods have been used, which may partly explain the inconsistent results across studies (32). Studies have differed with regard to the following parameters: 1) the period for which physical activity was assessed (i.e., childhood/adolescence, the year preceding the interview, lifetime, etc.), 2) the sources of physical activity (i.e., recreational activity, occupational activity, and/or activities of daily living), and 3) the various parameters of activity (i.e., frequency, duration, and intensity).

Studies differ in the recalled period of activity. Most cohort studies on physical activity and breast cancer confined their measurement of physical activity to the year preceding cohort.
entry. However, the majority of case–control studies measured physical activity over the year preceding diagnosis; some studies also included addition of information on an earlier period. In this study, we collected information on lifetime recreational activity, which enabled us to examine the effects of physical activity in different time windows, as well as the effects of changes in activity pattern. To date, only one case–control study (9) assessed lifetime recreational activity. In that study, the average frequency (hours per week) over a lifetime was calculated, but the authors did not account for changes in activities.

A failure to include all sources of physical activity, which is the case in most studies except one (22), may have resulted in misclassification. In our case–control study, we measured both recreational and, in smaller detail, occupational activities. The information on occupational activity was limited to the title of the occupation in which a woman had worked for the longest period, neglecting unpaid jobs, household activities, or other activities of daily living.

We collected extensive information on three parameters of lifetime recreational physical activity (i.e., lifetime duration, frequency, and intensity), as was done in more or less detail in two thirds of all studies of physical activity and breast cancer (9–15,18,19,22–26). However, duration was measured as an overall period in years, and, within this overall period, average frequency was measured as times per week instead of hours per week. Thus, the calculation of an overall energy expenditure index, in which frequency, intensity, and duration are mathematically combined, was not possible.

The effect of misclassification on the ORs depends on the type of the exposure variable (dichotomous, discrete, or continuous). As far as dichotomous variables, such as ever having been engaged in recreational activities (yes/no), are concerned, differential misclassification is not a likely explanation of the reduced ORs that we found. Differential misclassification as the main explanation would imply that case subjects would have underreported their physical activities more frequently than control subjects. This does not seem very likely, since case subjects are generally assumed to be more aware of their health-related habits than control subjects. Nondifferential misclassification, caused for instance by overreporting of physical activity considered as vigorous by generally inactive women, may have resulted in some bias to the null value. For the discrete variables (duration, frequency, or intensity) that were derived from the original continuous variables, differential misclassification might have occurred even if the original variables were nondifferentially misclassified (33). The direction of this bias is hard to predict. Thus, a combination of both differential and nondifferential misclassifications may have obscured a trend in ORs for duration, frequency, and intensity. Furthermore, because of the possible misclassification of exposure, the stratified analysis should be interpreted cautiously. The only way to quantify the total misclassification in our study would be to validate the measurement of physical activity, which is hardly possible for lifetime measurements. This difficulty does not alter the fact that the validity of methods to assess lifetime physical activity should be examined in future research.

Selection bias may have occurred in our study because nonresponding control subjects tended to have had a less healthy lifestyle with regard to alcohol consumption and smoking habits than responding control subjects. Information on physical activity was not collected for nonresponders. If a higher level of physical activity were associated with a healthy lifestyle, the proportion of physically active women in our control group might have been artificially high because of a selective nonresponse. This is unlikely, however, since, among responding control subjects, active women had similar drinking habits and were smoking more than inactive women.

The overall 30% reduction in the risk of breast cancer for premenopausal women associated with recreational physical activity is in agreement with the findings of 16 studies (1,4–18) but is in contrast with the findings of other studies (19–26). We also observed a reduced risk of breast cancer in women who were more physically active than their peers at ages 10–15 years (around the age of menarche). The effect of physical activity during these years on the risk of breast cancer has been the subject of several studies that found either a reduced risk (9,11,15,23) or no effect (12,13,24–26).

Our analyses with regard to recreational physical activity in specific time windows showed that neither very early physical activity (before age 20 years) nor recent physical activity (last 5 years) was associated with a greater reduction in risk than physical activity in the intermediate period. Women who had been physically active only during adolescence appeared to have a (statistically nonsignificantly) reduced risk of breast cancer as adults. Furthermore, women who started recreational activities after age 20 years and women who started earlier and were active at older ages appeared to have similar reductions in risk. Because very few women in our study started recreational activity after age 30 years (10% of all active women), we were unable to determine whether a reduction in the risk of breast cancer was associated with recreational activity started later in adult life. So far, our data suggest that physical activity in any period of life, rather than during a specific period, appears to be relevant. This result is in agreement with the study by Bernstein et al. (9), which is the only other study that assessed lifetime recreational activity. In that study, the effect of physical activity was more pronounced when considering complete lifetime activity than restricting the analysis to the 10 years after menarche. Changes in activity pattern throughout life have not been considered in other studies.

In our study, increasing frequency, intensity, or lifetime duration of activity was not associated with a further decrease in the risk of breast cancer. The lack of a clear dose–response or duration–response relationship is consistent with the results of six studies (5,10,15,21,22,24) but disagrees with the results of other studies (9,11–14,16). This finding might be partly explained by possibly higher background levels of physical activity during (unmeasured) daily activities (i.e., walking or biking) in this Dutch population compared with, for instance, North American populations.

When we used a combined measure of occupational and recreational activities, there appeared to be a slightly greater reduction in the risk of breast cancer for women whose occupation involved less than or equal to 80% sedentary activity and who were also engaged in recreational activity. Although about one third of all studies has assessed both occupational and recreational activities (5,12,14,17,18,22), only a few studies (12,14,22) provided risk estimates for combined exposure categories. In these studies, the combined measurement was not associated with a further decrease in the risk of breast cancer.

Subgroup analyses showed that the reduction in risk associated with both recreational and job activities was greater (al-
though not statistically significantly) for lean women (BMI <21.8 kg/m²) than for women with a higher BMI. This result is consistent with the results from two studies (14,16) but not with results from seven studies (9,12,13,19,24–26) that found no effect of BMI.

Our data also showed that, for women with a family history of breast cancer compared with women without such a history, recreational physical activity was associated with decreased risk. However, no effect in women with a family history of breast cancer was seen in the other studies (13,24,26) evaluating this effect. Furthermore, the reduction in risk associated with physical activity was slightly greater among nulliparous women, which is in agreement with one study (16) but not with other studies (9,11–13,24,26). Women with a history of benign breast disease had a higher risk associated with physical activity, which is not found in the only other study that evaluated this effect (26). In general, these interaction effects should be cautiously interpreted and cannot be considered to reflect real differential effects unless strongly supported by other studies.

Several hypotheses have been put forward to explain the decreased risk of breast cancer associated with physical activity. One hypothesis is that physical activity may affect the risk of breast cancer by reducing the cumulative lifetime exposure to endogenous sex hormones (34). Increased levels of physical activity are associated with a delayed menarche, an earlier age at menopause, and anovulation, all of which are accompanied by a lower cumulative exposure to endogenous estradiol (35). Although we found no clear association among control subjects for age at menarche, regularity of menstrual cycles, and physical activity at a young age (data not shown), the greater reduction in risk among lean women might support this hypothesis. Compared with women who have a higher BMI, lean women may more often experience anovulatory cycles when engaged in vigorous physical activity.

A second hypothesis is that physical activity affects the risk of breast cancer through its effect on body weight and body fat distribution (14). However, in premenopausal women with breast cancer, a high BMI is strictly protective, and the impact of weight gain throughout life on the risk of breast cancer for premenopausal women is unclear (36,37). On the other hand, larger amounts of abdominal fat, which is associated with a lack of physical activity in a few experimental and cross-sectional studies (38), might increase the risk of breast cancer in both premenopausal and postmenopausal women (39,40). In our study among mainly premenopausal women, neither a low waist-to-hip ratio nor weight loss at any time during adult life was associated with a decreased risk of breast cancer (data not shown). Furthermore, adjustment for BMI did not affect the ORs associated with physical activity.

A third hypothesis states that physical activity might lower plasma concentrations of insulin-like growth factor-I, possibly mediated by a negative energy balance (41,42). A recent publication from the Nurses’ Health Study (43) showed a positive association between plasma levels of insulin-like growth factor-I and the risk of breast cancer in premenopausal women (top versus bottom tertile: relative risk = 2.33; 95% CI = 1.06–5.16). So far, to our knowledge, no epidemiologic studies have examined physical activity and insulin-like growth factor-I levels simultaneously in relation to the risk of breast cancer.

Finally, moderate physical activity may enhance the immune system by elevating the number of natural killer cells, circulating lymphocytes, granulocytes, monocytes, and macrophages, whereas exhaustive physical exercise may depress immunologic function (3,44). It is unclear whether this effect is relevant because a role of the immune system in breast cancer carcinogenesis has not been demonstrated in epidemiologic studies (45).

In conclusion, this study of mainly premenopausal women confirms that physical activity appears to be associated with a reduction in the risk of breast cancer. We also found that vigorous recreational physical activity and the more moderate, generally practiced, levels of recreational activity appear to be protective. Leaner women appear to have a lower risk associated with physical activity than more obese women. Participation in recreational physical activity in any period of life, rather than during a specific period, appears to be relevant, implying that women who start with recreational physical activity at later ages may still benefit from their efforts. In future research, attempts should be made to examine the association between all sources of physical activity during life, including also daily activities as well as recreational and occupational activities, and the risk of breast cancer. For making public health recommendations, it is particularly important to examine when the initiation of physical activity still has an impact on the risk of breast cancer.

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NOTES

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