REVIEW

Recreational and Occupational Physical Activities and Risk of Breast Cancer

Marilie D. Gammon, Esther M. John, Julie A. Britton *

Physical activity has been hypothesized to reduce breast cancer risk, but an inverse association has not been consistently reported. In this review, we critically evaluate for coherence, validity, and bias the epidemiologic studies on recreational or occupational physical activity, discuss the biologic plausibility of the association, and identify areas for future research. Results from seven of nine studies suggest that higher levels of occupational physical activity may be associated with a reduction in risk, at least among a subgroup of women. Eleven of 16 investigations on recreational exercise reported a 12%–60% decrease in risk among premenopausal and postmenopausal women, although a dose–response trend was not evident in most of the studies. The reduction in risk associated with exercise was more likely to be observed in case–control studies than in cohort studies. Most investigations incompletely assessed physical activity, which contributed to conflicting findings on the optimal time period, duration, frequency, or intensity of activity to minimize risk. Physical activity may exert its effects through changes in menstrual characteristics, reduced body size, or alterations in immune function. In summary, most epidemiologic studies of physical activity reported a reduction in the risk of breast cancer among physically active women. Future research studies should focus on using a cohort design to rule out recall bias as a possible explanation for the decrease in risk associated with exercise, on improving assessment of lifetime physical activity from all sources to clarify whether there is a dose–response relation or an optimal time period, duration, frequency, or intensity of activity, and on elucidating the underlying mechanisms for the inverse association.


This review updates and evaluates the epidemiologic studies on recreational and occupational physical activities and breast cancer development, which have increased in number by more than twofold since the last complete reviews were undertaken (4,9,12), in order to identify areas for future research.

Methods

Literature Reviewed

To identify epidemiologic studies on physical activity and breast cancer, we performed computerized searches of the Medline biomedical literature database (National Library of Medicine, Bethesda, MD) for all years from 1966 on. The bibliography of previously published articles on the subject was reviewed. For very recent publications, the tables of contents of relevant journals located at Columbia University Health Sciences Library were examined. We included only articles based on epidemiologic studies and published in English. Studies reported only in the form of abstracts were identified but not formally reviewed because of the lack of sufficient information required for an adequate evaluation. Multiple articles based on the same source population are noted, where appropriate.

Evaluation Criteria

To evaluate the association between physical activity and breast cancer, we considered the following criteria: First, we reviewed the epidemiologic studies that addressed the association between breast cancer risk and either recreational or occupational physical activity in an attempt to identify consistencies and inconsistencies in the results and to elucidate the reasons behind the differences across studies. Second, we briefly reviewed other studies on alterations in menstrual characteristics, body size, serum hormone levels, and immune function to assess the biologic plausibility of the hypothesized inverse association (4,10,13–16) and to determine whether these studies can help to identify a biologically plausible time period for engaging in physical activity, if any, or the optimal intensity, frequency, or duration of the exercise necessary to prevent development of breast cancer. Lastly, we have summarized our results to identify areas in need of future research.

In reviewing the available epidemiologic studies, as well as the relevant literature on the biologic plausibility of the association, we considered the menopausal status of the study participants and whether the activity was from recreational or occupational sources. For evaluation of the relevant epidemiologic investigations, additional considerations included the following: the magnitude of association by type of study design (cohort or case–control) and the source of...
study participants; whether there was an optimal time period, duration, and intensity of physical activity (discussed in more detail below); whether risk was higher among subgroups of women based on factors other than menopausal status, such as body size or parity; and whether there was a dose–response trend (i.e., whether risk decreased with increasing levels of physical activity). Furthermore, methodologic differences (such as size of the sample, subject follow-up and response rates, whether potential confounding effects were considered, and issues regarding exposure assessment) were explored to determine their possible influence on any variation in results noted across studies.

Assessing physical activity in epidemiologic studies is complex and difficult (8,17). Issues that affect adequate assessment include the following: consideration of all sources of physical activity, such as recreation, occupation, and activities of daily living; the definition of physical activity that is used; the time of life when an individual is engaged in physical activity; and design issues that are inherent to cohort or case–control studies.

Inadequate assessment of physical activity could have resulted in misclassification of exposure and, ultimately, in inconsistent results across studies. Failure to have included all sources of physical activity (e.g., occupation, leisure time, and daily living) may have contributed to exposure misclassification. However, most studies of physical activity and breast cancer limited their assessments to either recreational or occupational sources and occasionally to both.

Complete assessment from any one source includes measurement of the following three major components that define physical activity: 1) the frequency (e.g., episodes per week), 2) duration (e.g., minutes or hours per episode), and 3) intensity (e.g., the strenuousness of each episode) (17). However, measurement of all three components in an epidemiologic study or the use of a valid or reliable instrument is not common (4). Duration or frequency of an activity is generally more easily obtained in epidemiologic studies than is intensity. Instead, indirect measures of intensity, based on the type of recreational exercise, have been assessed with varying degrees of thoroughness, but no investigation examining the risk of breast cancer has directly measured intensity (4). Measurement of an individual’s energy expenditure is virtually impossible in an epidemiologic study; however, adjusting for the effect of body mass has been found to greatly reduce any variations in energy expenditure resulting from individual differences by age, race, and sex (18).

Breast cancer risk may be affected by the time period in a woman’s life during which she was exposed to a risk factor or a protective factor (19). Thus, the timing of physical activity may be crucial. As discussed in the section below on biologic plausibility, exercise during the years of preadolescence, adolescence, or early adulthood may be important if physical activity affects breast cancer through changes in menstrual characteristics. Alternatively, persistent exercise throughout a woman’s life, or even recent activity, may be more important if the effect is through changes in body size or the immune system.

Even if physical activity is adequately measured by taking into account frequency, duration, and intensity of all activities from all sources, features of the epidemiologic design may also affect misclassification of exposure. Most cohort studies limit their assessment of physical activity to a single measure at baseline. Neither past nor subsequent changes in behavior are usually assessed. In case–control studies, difficulties with long-term recall, including differential recall by case–control status, are always of concern.

Review of Epidemiologic Studies

Recreational Physical Activity

Table 1 outlines 16 studies that have been published on recreational physical activity in relation to breast cancer (20–35). Of these, all but five (21,23,24,33,35) of these studies reported that recreational exercise reduces the risk of developing breast cancer at least among one subgroup of women. The evidence, however, is inconsistent on several key issues. First, it is unclear whether all women who exercise are at decreased risk (20,26,28,29,31,34) or whether the risk reduction is restricted to premenopausal (25,27,32) or postmenopausal (22,30) women. The magnitude of the risk reduction ranged from 12% to 60% among the various studies. However, whether risk decreases with increasing levels of physical activity was inconsistent across studies. In addition, it is not well understood whether the timing, frequency, duration, or intensity of the exercise is critical to reduce risk.

Six additional reports (36–41) on this topic have been published as abstracts or have been mentioned in a previous review but have not yet been published as manuscripts. One was a hospital-based case–control study (36), two were population-based case–control studies (37,38), and three were prospective cohort studies (39–41). Except for one report of an increased risk (36), these investigations found a decrease in risk that ranged from 12% to 80%. Without more detail, we were unable to place these additional studies in tabular form or to appraise them adequately. Also, one investigator published two reports on data from the same study (20,42); we present data from the more recent article (20). Below, we have focused on the 16 studies that have been published as manuscripts and on issues that may clarify the inconsistencies among them.

Study Design and Population

Frisch and colleagues (20) were the first to report on the association between recreational exercise and breast cancer risk. Using data from a retrospective cohort study, they noted that risk was reduced by nearly 50% among women of all ages who had participated in intramural sports during college. Results from one prospective cohort study by Thune et al. (34) also reported a statistically significant decrease in risk of 37% among young women of all ages. Paffenbarger et al. (23) found a nonsignificant 12% risk reduction among college alumni in relation to adult exercise. However, no association was reported by two investigations; one was another study conducted by Paffenbarger et al. (21) that was a retrospective cohort of college alumni and used college records to assess exercise, and the other was a study by Albanes et al. (22) that included participants of all ages in a U.S. national follow-up study. In contrast, Dorgan et al. (24), using data from the Framingham Heart Study, found a borderline statistically significant 20% increase in risk among mostly postmenopausal women.

The remaining 10 studies (25–33,35) were recently published case–control investigations. With two exceptions—population-based studies conducted in Washington State (33) and several locations in the United States (35)—population-based studies (25,26,28,30) and hospital-based studies (27,29,31,32) conducted internationally have reported a decrease in risk associated with recreational activity. The risk reduction ranged from 27% to 60% in the population-based studies and from 26% to 47% in the hospital-based studies.

Sample Size

Although the total number of women enrolled in the cohort studies may have been quite high, the number of case subjects with breast cancer was usually low. For example, in early cohort studies, the number of case subjects ranged from 69 (42) to 122 (22). Only the most recently published cohort study (34) was based on a more adequate sample of 351 case subjects. In contrast, with the exception of one study that included only 157 case subjects (32), the number of cases included in the case–control studies was generally much higher, ranging from 444 (26) to 6631 (28). Thus, the smaller numbers of case subjects in the cohort studies may have yielded relatively unstable estimates of
Table 1. Selected results from 16 studies on recreational physical activity and breast cancer risk

<table>
<thead>
<tr>
<th>First author, year (reference No.)</th>
<th>Study design and population</th>
<th>Assessment of physical activity</th>
<th>Measure of association*</th>
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</thead>
<tbody>
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<td></td>
<td></td>
<td>Timing</td>
<td>Estimate of effect by menopausal status or age</td>
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<tr>
<td>Frisch 1987 (20)</td>
<td>Retrospective cohort study U.S. colleges (USA) 5398 living alumnae who graduated between 1925 and 1981 Follow-up 1925–1981 69 prevalent cases†</td>
<td>Participation in sports from college records College Participation in sports Non-athlete versus athlete aRR (95% CI) Pre &amp; Post 1.86 (1.00—3.47)</td>
<td>Adjusted for: age, age of menarche, family history of cancer, leanness, number of pregnancies, oral contraceptive use, smoking, and use of hormones for menopausal symptoms Also considered: age of first live birth, age of natural menopause, breast cancer in mother, breast cancer in sister, cancer in mother, ever pregnant, height, hysterectomies, now exercising regularly, now on low-fat diet, now restricting diet, nulliparity, number of live births, number of pregnancies, percent fat, precollege training, and weight</td>
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<tr>
<td>Paffenbarger, 1987 (21)</td>
<td>Retrospective cohort study University of Pennsylvania (USA) 4706 women who graduated between 1916 and 1950 Follow-up 1916–1978 62 incident cases†</td>
<td>Participation in sports from college records College Hours/week ≥5 versus &lt;5 aRR (P) Pre &amp; Post 0.96 (.92)</td>
<td>Adjusted for: age and year of birth Also considered: none</td>
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<tr>
<td>Albanes, 1989 (22)</td>
<td>Prospective cohort study NHANES§ I Epidemiologic Follow-up Study, (USA) 7413 women aged 25–74 y at baseline, 1971–1975 Follow-up 1971–1984 122 incident cases 46 premenopausal case subjects</td>
<td>Self-assessment score score Usual day at baseline Self-assessment score None/little versus much None/little versus much None/little versus much aRR (95% CI) Pre &amp; Post 1.0 (0.6–1.6) P for trend = .98 Pre 0.6 (0.3–1.2) Post 1.7 (0.8–2.9)</td>
<td>Adjusted for: age Also considered: age at first birth, age at menarche, age at menopause, body mass index, dietary fat intake, employment status, family history of breast cancer, general health status, length of follow-up before diagnosis of breast cancer, and parity</td>
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<tr>
<td>Paffenbarger, 1992 (23)</td>
<td>Prospective cohort study University of Pennsylvania (USA) 2370 alumnae aged 40–50 y at baseline in 1962 Follow-up 1962–1977 73 incident cases†</td>
<td>Self-reported the type, frequency, and duration (hours/week) of activities; number of city blocks walked and stairs climbed daily Ages 40–50 y Kilocalories/week ≥1000 versus &lt;1000 aRR (95% CI) Pre &amp; Post 0.88 (0.54–1.43)</td>
<td>Adjusted for: age, body mass index, and history of maternal cancer Also considered: none</td>
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### Table 1—continued. Selected results from 16 studies on recreational physical activity and breast cancer risk

<table>
<thead>
<tr>
<th>First author, year (reference No.)</th>
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<th>Adjustment for confounding</th>
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<tr>
<td><strong>Prospective cohort studies</strong></td>
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<td>Dorgan, 1994 (24)</td>
<td>Prospective cohort study</td>
<td>Framingham Heart study (USA)</td>
<td>aRR (95% CI)</td>
<td>Adjusted for: age, age at first pregnancy, alcohol consumption, education, menopausal status, number of live births, and occupation</td>
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<td>2298 women aged 35–68 y at fourth examination in 1954–1956</td>
<td>Pre &amp; Post 1.2 (1.0–1.6)</td>
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<td>Follow-up 1954–1984</td>
<td>Post Not available; estimates similar to combined groups</td>
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<td>117 incident cases</td>
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<td>5 premenopausal case subjects</td>
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<td>Self-reported usual day at baseline hours spent at sleep/rest, sedentary/ slight, and moderate/heavy activities</td>
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<td><strong>Timing</strong></td>
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<td>One hour spent at Moderate/heavy versus sleep/rest</td>
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<td><strong>Estimate of effect by menopausal status or age</strong></td>
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<td>Pre &amp; Post 1.2 (1.0–1.6)</td>
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<td>Adjusted for: age, age at first pregnancy, alcohol consumption, education, menopausal status, number of live births, and occupation</td>
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<td>Also considered: body mass index, height, postmenopausal exogenous hormone use, and weight</td>
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<tr>
<td>Thune, 1997 (34)</td>
<td>Prospective cohort study</td>
<td>National Health Screening Service (Norway)</td>
<td>aRR (95% CI)</td>
<td>Adjusted for: age at study entry, body mass index, county of residence, height, and number of children</td>
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<td>25 624 women aged 20–58 y at baseline, 1977–1983</td>
<td>Pre &amp; Post 0.63 (0.42–0.95)</td>
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<td>Follow-up 1977–1994</td>
<td>Post P for trend = .04</td>
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<td>351 incident cases</td>
<td>Pre 0.67 (0.41–1.10)</td>
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<td>100 premenopausal case subjects</td>
<td>Post P for trend = .15</td>
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<td>Self-assessment score</td>
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<td>Year preceding baseline interview</td>
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<td>Regular versus sedentary</td>
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<td>aRR (95% CI)</td>
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<td>Pre &amp; Post 0.63 (0.42–0.95)</td>
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<td>Pre P for trend = .04</td>
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<td>Post 0.67 (0.41–1.10)</td>
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<td>Adjusted for: age at study entry, body mass index, county of residence, height, and number of children</td>
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<td>Also considered: age at birth of first child, daily energy intake, fiber intake, high-density lipoprotein (HDL) cholesterol, ratio of total cholesterol to HDL cholesterol, smoking, total daily fat intake, triglycerides, and &lt;45 versus ≥45 years of age at study entry</td>
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<td>Population-based case–control studies</td>
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<td>Bernstein, 1994 (25)</td>
<td>Population-based case–control study</td>
<td>Los Angeles County (USA) 545 cases diagnosed 1983–1989</td>
<td>aOR (95% CI)</td>
<td>Adjusted for: age at first full-term pregnancy, age at menarche, birth date, first-degree family history of breast cancer, months of lactation, number of full-term pregnancies, parity, Quetelet’s index at reference date, race, and total months of oral contraceptive use</td>
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<td>545 control subjects</td>
<td>Pre 0.70 (0.47–1.06)</td>
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<td>(neighborhood)</td>
<td>P for trend = .027</td>
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<td>Aged ≤40 y at reference date</td>
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<td>Presumably all women</td>
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<td>premenopausal since ≤40 y</td>
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<td>Self-reported name, hours/week, and start and stop ages of activities</td>
<td>aOR (95% CI)</td>
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<td>Time period</td>
<td>Pre 0.70 (0.47–1.06)</td>
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<td>Hours/week</td>
<td>P for trend = .027</td>
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<td>≥5.6 versus none</td>
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<td>Lifetime history</td>
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<td>≥3.8 versus none</td>
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<td>Adjusted for: age at first full-term pregnancy, age at menarche, birth date, first-degree family history of breast cancer, months of lactation, number of full-term pregnancies, parity, Quetelet’s index at reference date, race, and total months of oral contraceptive use</td>
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<td>Also considered: average number of months between full-term pregnancies, employment status, invasive breast cancer only, marital status among nulliparous women, months between first and last full-term pregnancy, months since last full-term pregnancy, and Quetelet’s index at 18 years of age</td>
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<th>Estimate of effect by menopausal status or age</th>
<th>Adjustment for confounding</th>
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<tbody>
<tr>
<td>Friedenreich, 1995 (26)</td>
<td>Population-based case–control study Adelaide (Australia) 444 cases diagnosed 1982–1984 444 control subjects (electoral rolls) Aged 20–74 y at reference date 110 premenopausal case subjects</td>
<td>Self-reported hours/week participating in light, moderate, and vigorous activities separately for summer and winter activities</td>
<td>Year prior to diagnosis</td>
<td>Kilocalories/week</td>
<td>aOR (95% CI) Pre &amp; Post 0.73 (0.50–1.05) P for trend = .09 Pre 0.60 (0.30–1.17) P for trend = .09 Post 0.73 (0.44–1.20) P for trend = .32</td>
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<tr>
<td>Mittendorf, 1995 (28)</td>
<td>Population-based case–control study Western Massachusetts, Maine, New Hampshire, and Wisconsin (USA) 6631 cases diagnosed 1988–1991 9094 control subjects (driver’s license and HCFA§) Aged &lt;75 y at reference date 31% of women premenopausal</td>
<td>Self-reported name and frequency of ≤3 strenuous physical activities or team sports</td>
<td>Ages 14–22 y Frequency of strenuous activity/year</td>
<td>≥364 versus none</td>
<td>aOR (95% CI) Pre &amp; Post 0.5 (0.4–0.7) P for trend = .02 Post not available; estimates similar to combined groups</td>
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<tr>
<td>McTiernan, 1996 (30)</td>
<td>Population-based case–control study Northwestern Washington State (USA) 537 cases diagnosed 1988–1990 492 control subjects (RDD) Aged 50–64 y at reference date 44 premenopausal case subjects</td>
<td>Self-reported name, frequency (months/year and times/week or month), duration per episode, as well as start and stop ages of activities participated in ≥24 times/year</td>
<td>Age periods Hours/week</td>
<td>≥3.0 versus none</td>
<td>aOR (95% CI) Pre &amp; Post 1.0 (0.95–1.0) P for trend = .92 1.1 (0.7–1.6) P for trend = .29 Pre Not available; associations stronger in postmenopausal women Post 0.8 (0.5–1.3) P for trend = .03</td>
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Adjusted for: date of birth, energy intake, and Quetelet’s index Also considered: age at first full-term pregnancy, age at menarche, cigarette smoking, education, family history of breast cancer, history of bilateral oophorectomy, menopausal status, number of live births, use of oral contraceptives, personal history of benign breast disease, and use of hormone replacement therapy

Adjusted for: age, age at first birth, age at menarche, age at menopause, body mass index, family history of breast cancer, history of benign breast disease, interaction between menopausal status and body mass index, menopausal status, parity, recent alcohol consumption, state of residence, and type of menopause Also considered: none

Adjusted for: age and education Also considered: age at first full-term pregnancy, age at menarche, alcohol consumption, body mass index, dietary fat intake, education, family history of breast cancer, menopausal status, number of full-term pregnancies, number of previous screening mammograms, previous benign breast disease, use of oral contraceptives, and use of hormone replacement therapy
<table>
<thead>
<tr>
<th>First author, year (reference No.)</th>
<th>Study design and population</th>
<th>Assessment of physical activity</th>
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<tr>
<td>Chen, 1997 (33)</td>
<td>Population-based case–control study Three-county Seattle Metropolitan Area (USA) 1983–1990 747 cases diagnosed 961 control subjects (RDD) Aged 21–45 y at reference date 643 premenopausal case subjects</td>
<td>Self-reported name, frequency (months/year and times/week or month), and duration (hours and/or minutes), as well as timing of activity participated in on a regular basis (&gt;2/mo in any year)</td>
<td>Hours/week aOR (95% CI) Adjusted for: age, also considered: age at first-term pregnancy, age at menarche, alcohol consumption, body mass index, county of residence, education, family history of breast cancer, family income, marital status, menopausal status, parity, and smoking status</td>
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<tr>
<td>Gammon, 1998 (35)</td>
<td>Population-based case–control study Atlanta, Seattle, New Jersey (USA) 1990–1992 1647 cases diagnosed 1501 control subjects (RDD) Aged &lt;45 y at reference date 1474 premenopausal case subjects</td>
<td>Self-reported frequency per week or month of moderate and vigorous activities; participation in sports to keep weight low</td>
<td>Relative units/week aOR (95% CI) Adjusted for: adult body mass index, age at first birth, age at menarche, body mass index at age 20, caloric intake in past year, center, education, family income, family history of breast cancer, family history of breast biopsy, lactation, marital status, use of menopausal estrogens, menopausal status, number of abstractions, number of miscarriages, oral contraceptive use, parity, race, smoking, and usual alcohol consumption Also considered: chemotheraphy, frequency of breast self-examinations and mammography, interval of time between interview and reference date, and stage</td>
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<td>Taioli, 1995 (27)</td>
<td>Hospital-based case–control study Geographic location not available 1987–1990 531 control subjects (non-tobacco- or alcohol-related diseases) All ages at reference date 196 premenopausal case subjects</td>
<td>Self-reported name, frequency (months/year and number of years), and duration per episode of ≤2 activities from a list of 26 activities</td>
<td>Hours/week aOR (95% CI) Adjusted for: age, age at menarche, body mass index, education, hospital of admission, pregnancies, race, and year of interview Also considered: age at first birth and marital status</td>
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<td>Hirose, 1995 (29)</td>
<td>Hospital-based case-control study Nagoya (Japan)</td>
<td>Participation in exercise for health</td>
<td>aOR (95% CI) Pre &amp; Post</td>
</tr>
<tr>
<td></td>
<td>1186 cases diagnosed 1988–1992 23 163 control subjects (non-cancer conditions) Aged 18+ y at reference date 607 premenopausal case subjects</td>
<td>Not specified Times/week ≥2 versus none</td>
<td>0.74 (0.55–0.99) 0.72 (0.53–0.97)</td>
</tr>
<tr>
<td>D’Avanzo, 1996 (31)</td>
<td>Hospital-based case–control study Milan, Genoa, Naples, and provinces of Pordenone, Gorizia, Forli, Latina (Italy)</td>
<td>Self-reported duration of leisure time activity in predefined categories: &lt;2, 2–4, 5–7, 7+ hours/week</td>
<td>aOR (95% CI) Pre &amp; Post</td>
</tr>
<tr>
<td></td>
<td>2569 cases diagnosed 1991–1994 2588 control subjects (non-cancer conditions) Aged 20–74 y at reference date 988 premenopausal or perimenopausal case subjects</td>
<td>Age periods Hours/week &gt;7 versus &lt;2</td>
<td>0.94 (0.77–1.16) 0.77 (0.56–1.06) 0.68 (0.40–1.09)</td>
</tr>
</tbody>
</table>

Also considered: age at first full-term pregnancy, age at menarche, alcohol consumption, average months of breast feeding, body mass index, breast cancer among first-degree relatives, controlled diet, delivery, dietary factors (bean curd, beef, boiled or broiled fish, carrots, chicken, egg, fruits, green vegetables, ham, milk, miso soup, number of rice bowls per day, pork, potato, raw vegetables, sashimi, sausage, sweet potatoes, and sweet dessert), height, marital status, menstrual regularity, number of births, passive smoking, preference for saltiness, preference for fatty food, sleeping time, smoking, type of breakfast, and weight.
Follow-up and Response Rates

Follow-up rates in the cohort studies appear adequate, ranging from 71% (20) to 91% (34), although rates were not reported for two (21,23). In the case–control studies, response rates also appear satisfactory, thus minimizing selection bias and increasing generalizability. The population-based case–control studies showed little variation in rates, with about 80% of case subjects and about 75% of control subjects agreeing to participate (25,26,28,30,33,35). Hospital-based case–control studies reported more variation, ranging from 68% (32) to 96% (31) among case subjects, with a similar range among control subjects. One hospital-based study (27) did not provide response rates.

Overall, the findings do not appear to vary with follow-up or response rates. The third of studies that do not support a decrease in risk with increased exercise levels (21,23,24,33,35) are not among those few studies that reported relatively low follow-up or response rates.

Confounding

As noted in Table 1, the vast majority of studies were able to adjust the analyses for potential confounding factors. However, it is possible that assessment of confounding factors in cohort studies may have been inadequate if exposure patterns changed during follow-up. Also, exercisers and non-exercisers may differ on other important health-related characteristics, such as energy intake, vegetable and fruit consumption, or body size. Valid and precise measurement of these factors is very difficult in epidemiologic studies, which would result in inadequate control of their confounding effects. Nevertheless, it is not apparent that confounding, or even incomplete control of confounding, has contributed to any inconsistent results observed across studies.
greater extent than case subjects. Nevertheless, it seems unlikely that overestimation of past exercise would have occurred more often in control subjects than in case subjects in most case–control studies, given the wide variation in age and geographic location of participants across studies.

One investigation (43) addressed the possibility of bias in long-term recall of physical activity. Physical activity was assessed in 1960 among participants in a cohort study, and 137 were re-interviewed in 1992–1996. Long-term recall was better among women than among men, but participants with higher levels of current activity tended to overestimate past activity, and younger women tended to underestimate past levels (43). Thus, inaccurate long-term recall is a possible explanation for the inconsistent results noted between cohort and case–control investigations.

Definition of physical activity. The early cohort studies (20–23) did not quantify the components of frequency, duration, or intensity that define exercise. Although the subsequent cohort studies and the case–control studies have more adequately assessed these components, the results remain unclear on the optimum levels of each that is required to reduce a woman’s risk of breast cancer. Bernstein et al. (25) found a risk reduction of 60% in relation to 3.8 hours or more per week of all recreational exercise combined, and D’Avanzo et al. (31) reported a 32% reduction for more than 7 hours per week. In contrast, McTiernan et al. (30) and Chen et al. (33) found no reduction in risk in relation to the highest quartile of exercise of at least 4 or more hours of exercise per week, respectively. Of nine studies that reported on exercise intensity, five investigations (26,28,30,32,34) reported a 30%–50% reduction in relation to vigorous exercise, although the number of hours per week needed to benefit from this decrease in risk was not often specified. Four other investigations (24,27,33,35) did not find a reduction with vigorous or moderate activity.

Timing of physical activity. A few case–control studies (25,31–33,35) have examined the effects of exercise at multiple points during a woman’s lifetime and have yielded inconsistent results. For example, D’Avanzo et al. (31) found that more than 7 hours a week of exercise at ages 30–39 years or 50–59 years reduced breast cancer risk, but equally heavy exercise at ages 15–19 years did not. Hu et al. (32) reported that expenditure of 1100 kilocalories/week or more during a woman’s third decade reduced risk by 47% among postmenopausal women, whereas similarly high exercise during the teenage years elevated risk by 39%. Other investigations (33,35) that examined the effects of exercise at multiple points in a woman’s life have not observed a decrease with any time period.

Considering a single period in a woman’s life also reveals inconsistent findings across studies. Nine studies (20,21,25,27,28,31–33,35) have assessed exercise during the teen years; three (20,25,28) showed statistically significant reductions in breast cancer risk, and six (21,27,31–33,35) reported little or no reduction. Twelve studies (22–26,29–35) assessed exercise sometime during the adult years; five (25,26,30,31,34) observed a decrease in risk, five (23,29,32,33,35) showed no effect, and two (22,24) reported an increase in risk.

Only the study by Bernstein et al. (25) assessed lifetime activities. Among premenopausal women, the average lifetime activity, but not the specific timing of the physical activity, was related to a reduction in risk. Thus, although there is some biologic plausibility that participation in exercise at certain times in a woman’s life may be important in determining her risk for breast cancer, the currently published literature is inconsistent as to which period or periods are the most relevant, if any, or if persistent exercise is the most optimal behavior for decreasing risk.

Subgroup Analyses

Although the majority of studies on recreational exercise show a reduced risk, in many investigations this decrease was limited to only one subgroup of women, whereas no association was found overall or in other subgroups. These generally inconclusive findings led investigators of many reports to conclude that exercise had little or no effect on breast cancer risk.

In one case–control study (30), for example, risk for middle-aged women was increased by 10% for more than 5 hours of activity/week, but the estimate of effect was not statistically significant and there was no dose–response trend. Only in postmenopausal women did a statistically significant inverse trend become evident. However, the modest 20% decrease associated with the highest level of activity was not statistically significant. The authors concluded that their data were only weakly supportive of a protective role for physical activity. Similarly, in a cohort study (22), there was no association with high levels of recreational exercise among all women combined. However, a decrease was observed for postmenopausal women, whereas an increase was noted for premenopausal women, although neither result was statistically significant. The authors concluded that it was unlikely that physical activity was related to risk.

Comparing results across studies by subgroups can be instructive. Among investigations that examined risk among premenopausal women, three (25,29,34) found a statistically significant decrease, three (26,27,32) observed a nonsignificant reduction, two (33,35) reported no association, and one (22) found a nonsignificant increase. Overall, these findings support a reduced risk for exercise among premenopausal women. Among studies that considered risk in postmenopausal women, three (28–30) found a statistically significant decrease, three (22,26,34) observed a nonsignificant reduction, one (27) found no association, and two (24,32) saw an increase. Again, these results suggest a decreased risk among postmenopausal women. In contrast, findings are inconsistent when studies that included women of all ages are considered. Five studies (20,26,28,31,34) reported a decrease in risk, five (22,23,30,32,33) reported no association, and one study (24) reported an increased risk.

Several investigators have also examined whether other subgroups of women are at a reduced risk of breast cancer in relation to physical activity, but few subgroups have been identified and none consistently across studies. Bernstein et al. (25) noted that risk was reduced by 72% among parous women and by only 27% among nulliparous women. However, other investigators (28,30,33,35) have not corroborated this observation. Also, Thune et al. (34) found that risk was statistically significantly decreased by 72% among women in the lowest tertile of the body mass index at baseline as compared with 17% among those in the highest tertile. Other investigators (25,30,33,35) have not found a lower risk among leaner women.
**Dose–Response Effect**

Among five studies (20,26,28,31,34) that support the hypothesis that exercise protects against breast cancer among all women, regardless of their menopausal status, a statistically significant decreasing trend with increasing activity was noted in two studies (28,34) and this decreasing trend was of borderline statistical significance in a third (26). Of the six studies (25–27,29,32,34) that showed a decrease in risk among premenopausal women, only one (25) showed a statistically significant trend, and two (26,34) reported a trend that was of borderline statistical significance. Of the six studies (22,26,28–30,34) that showed a reduction in risk among postmenopausal women, only two (28,30) found a statistically significant dose–response trend. It is possible that the association between exercise and breast cancer risk is not linear but may have a threshold.

**Occupational Physical Activity**

Table 2 presents 11 reports (22,24,31,34,44–50) that have been published on the risk of breast cancer in relation to occupational physical activity; two of these reports (47,49) are updates of the original reports (22,45). Although there were inconsistencies in the results, these studies suggest that there may be a decrease in risk associated with occupational physical activity. Five studies (31,34,44,46,50) reported statistically significant reduced risks at least among one subgroup of women with physically active jobs, two studies (47,49) found nonsignificant risk reductions among certain subgroups of women, and two studies (24,48) found no association. It needs to be resolved whether occupational physical activity protects against breast cancer in premenopausal women (47), postmenopausal women (49), or women of all ages (31,34,50).

**Study Design and Population**

A death certificate study from Washington State (44) and a record-linkage study from Shanghai (46) that used job title as a measure of physical activity found statistically significant reduced risks of breast cancer among women in physically active jobs. The comparison of working women to regional populations, however, raises concern whether the healthy-worker effect partly explains the lower risk observed in these two studies (44,46). A retrospective follow-up study of Finnish teachers (47) found a nonsignificant lower standard incidence ratio (SIR) among physical education teachers (SIR = 1.35) than among language teachers (SIR = 1.48).

Results from three prospective cohort studies (24,34,49), one population-based case–control study (50), and two hospital-based case–control studies (31,48) were inconsistent. The follow-up of a U.S. national cohort study (49) and a Turkish case–control study (48) found no association with occupational activity among women of all ages combined. Similarly, the Framingham Heart Study (24), which followed mostly postmenopausal women, found no association. In a large Norwegian follow-up study (34), risk was statistically significantly reduced by 52% among women who reported doing heavy manual labor during the year before the baseline interview. Also, two large case–control studies, one conducted in Italy (31) and the other in the United States (50), reported odds ratios ranging from 0.54 to 0.82 for the most active occupations.

Given the variety of study designs, it is difficult to compare the magnitude of the association across studies. In the three largest analytic studies (31,34,50), risk reductions associated with the highest level of work-related activity ranged from 18% to 52%.

**Sample Size**

The studies reporting on occupational physical activity vary widely in the number of case subjects with breast cancer included, ranging from 117 case subjects (24) to nearly 5000 case subjects (50). Limited sample size may have contributed to inconsistent results for postmenopausal women. The three largest analytic studies (31,34,50), however, found risk reductions among both premenopausal and postmenopausal women.

**Follow-up and Response Rates**

Follow-up rates were more than 90% in two Scandinavian studies (34,47). In the U.S. studies, the follow-up rate was also high for the U.S. National Health and Nutrition Examination Survey (NHANES) I follow-up study (87%) (22), but somewhat lower for the Framingham Heart Study (81%) (24). Response rates were very high in the Italian case–control study (96%) (31) and in the Chinese record-linkage study (98%) (46), but somewhat lower among case subjects (81%) and control subjects (84%) in the United States (50). One hospital-based case–control study (48) did not report response rates. Overall, the follow-up and response rates were high, thus minimizing selection bias.

**Confounding**

Lack of control for other factors in three studies (44,46,47) raises concern about potential confounding by socioeconomic status. If women in physically active jobs are of lower socioeconomic status, they may be at lower risk for breast cancer resulting from differences in other risk factors associated with socioeconomic status, such as reproductive characteristics. With the exception of the Turkish case–control study (48), adjustments for multiple risk factors were made in the other cohort (24,34,49) and case–control (31,50) investigations. It is therefore unlikely that the inconsistent results in these studies were due to confounding.

**Physical Activity Assessment**

The major difference between studies on occupational and recreational physical activities lies in exposure assessment. In several studies of occupational physical activity, job title was used as a measure of physical activity (44,46–48,50); in the remaining studies of this kind, participants were asked to rate their physical activity level at work (31,34,49) or investigators determined the subjects’ activity levels on the basis of the number of hours spent at various activities (24). Misclassification. Misclassification of exposure status could have contributed to the inconsistent results if the following occurred: a study participant’s physical activity level differs from the average activity level assigned to a specific occupation;
the self-assessed activity level is based on a subjective rather than on an objective rating system; the occupational activity levels (e.g., low) greatly differ from the recreational activity levels (e.g., high); and/or physical activity levels at work changed during the follow-up period. The latter issue is of particular concern in four cohort studies (24, 34, 47, 49) with a single baseline exposure assessment and a subsequent follow-up period that ranged from 17 (34) to 34 years (24). Unless baseline information is routinely updated, the case–control design might be better suited to address changes in exposures.

**Definition of physical activity.** None of the studies conducted a comprehensive exposure assessment that considered intensity, frequency, and duration of work-related activity. In some studies, intensity was based on average energy expenditure (44, 46, 48, 50) or average number of hours spent sitting (46, 48), which the investigators assigned to record-based or self-reported occupations, or was assumed by a comparison of a presumably active cohort (e.g., physical education teachers) to an inactive cohort (e.g., language teachers) (47). In other studies, work-related intensity was based on the self-reported number of hours spent in various activities during a usual day at baseline (24) or the rating provided by study participants (31, 34, 49).

**Timing of physical activity.** Most studies assessed occupational physical activity at a single point in time. The inves-

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### Table 2. Selected results from 11 studies on occupation physical activity and breast cancer risk

<table>
<thead>
<tr>
<th>First author, year (reference No.)</th>
<th>Study design and population</th>
<th>Assessment of physical activity</th>
<th>Timing</th>
<th>Estimate of effect by menopausal status or age</th>
<th>Adjustment for confounding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vena, 1987 (44)</td>
<td>Proportionate mortality study Washington State (USA) 25 000 women of all ages at death 1974–1979 791 deaths†</td>
<td>Occupation listed on death certificate</td>
<td>Usual occupation</td>
<td>Physical activity rating (U.S. Department of Labor) Pre &amp; Post</td>
<td>Adjusted for: none Also considered: none</td>
</tr>
<tr>
<td>Zheng, 1993 (46)</td>
<td>Linkage study Shanghai, China 1982 census population 2736 case subjects aged 30+ y at diagnosis in 1980–1984†</td>
<td>Self-reported occupation</td>
<td>At diagnosis or before retirement</td>
<td>Energy expenditure index (kJ/min) SIR (P) Pre &amp; Post</td>
<td>Adjusted for: none Also considered: none</td>
</tr>
</tbody>
</table>

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### Retroactive cohort studies

1. Vihko,‡ 1992 (45) Retrospective cohort study Finnish teachers (Finland) Graduated since 1920 Aged 20+ y at baseline 1,2 Job title listed in teacher registers 1,2 Job at baseline | Job title | SIR (95% CI) | Adjusted for: none Also considered (for subgroup): age at first birth of child, age at menarche, age at menopause, alcohol consumption, dietary factors (cereal products, coffee, fish, products, high-fat milk products, low-fat milk products, meat, products, sweet cakes, tea, vegetable oil, and vegetables), irregular menstruation, leisure time physical activity, prevalence of ovariectomy, prevalence of hysterectomy, smokers, social status, and total number of children |
| PE versus population | 1.28 (≥.05) | 20+ y |
| Ratio SIR<sub>PE</sub>/SIR<sub>L</sub> | 0.81 (≥.05) | 20–49 y |
| L versus population | 1.59 (≥.01) | 20–49 y |
| Ratio SIR<sub>PE</sub>/SIR<sub>L</sub> | 0.89 | 20–49 y |
| L versus population | 1.48 (1.27–1.69) | 20–49 y |
| Ratio SIR<sub>PE</sub>/SIR<sub>L</sub> | 0.73 | 20+ y |
| PE versus population | 1.01 (0.46–1.91) | 20+ y |
| Ratio SIR<sub>PE</sub>/SIR<sub>L</sub> | 0.99 | 20+ y |
| L versus population | 1.52 (1.00–2.21) | 20+ y |
| Ratio SIR<sub>PE</sub>/SIR<sub>L</sub> | 1.54 (1.28–1.83) | 20+ y |

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### Record-based studies

1. Proportionate mortality study Washington State (USA) 25 000 women of all ages at death 1974–1979 791 deaths†
2. Linkage study Shanghai, China 1982 census population 2736 case subjects aged 30+ y at diagnosis in 1980–1984†
3. Vihko,‡ 1992 (45)
4. Pukkala,‡ 1993 (47)
<table>
<thead>
<tr>
<th>First author, year (reference No.)</th>
<th>Study design and population</th>
<th>Assessment of physical activity</th>
<th>Timing</th>
<th>Measure of association*</th>
<th>Adjustment for confounding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective cohort studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3Albanes, 1989 (22)</td>
<td>Prospective cohort study NHANES I Epidemiologic Follow-up Study (USA)</td>
<td>Self-assessed intensity</td>
<td>Pre &amp; Post</td>
<td>aRR (95% CI)</td>
<td>Adjusted for: age at first birth, age at menarche, age at menopause, body mass index, dietary fat intake, employment status, family history of breast cancer, general health status, length of follow-up prior to diagnosis of breast cancer, and parity</td>
</tr>
<tr>
<td>4Steenland, 1995 (49)</td>
<td>7413 women aged 25–74 y at baseline, 1971–1975</td>
<td>Self-assessed intensity</td>
<td>Pre &amp; Post</td>
<td>aRR (95% CI)</td>
<td>Adjusted for: age at first birth, age at menarche, age at menopause, body mass index, dietary fat intake, employment status, family history of breast cancer, general health status, length of follow-up prior to diagnosis of breast cancer, and parity</td>
</tr>
<tr>
<td>3Follow-up 1971–1984 122 incident cases 46 premenopausal case subjects</td>
<td></td>
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</tr>
<tr>
<td>4Follow-up 1971–1987 163 incident cases†</td>
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<tr>
<td><strong>Dorgan, 1994 (24)</strong></td>
<td>Prospective cohort study Framingham Heart Study (USA) 2298 women aged 35–68 y at 4th examination in 1954–1956 Follow-up 1954–1984 117 incident cases 5 premenopausal case subjects</td>
<td>Self-reported hours spent at sleeping and sedentary, slight, moderate, and heavy activities during workdays</td>
<td>Pre &amp; Post</td>
<td>aRR (95% CI)</td>
<td>Adjusted for: age at first pregnancy, alcohol consumption, education, menopausal status, number of live births, and occupation Also considered: body mass index, height, postmenopausal estrogen hormone use, and weight</td>
</tr>
<tr>
<td>Thune, 1997 (34)</td>
<td>Prospective cohort study National Health Screening Service (Norway) 25 624 women aged 20–58 y at baseline 1977–1983 Follow-up 1977–1994 351 incident cases 100 premenopausal case subjects</td>
<td>Self-assessed intensity of work</td>
<td>Year preceding baseline interview</td>
<td>aRR (95% CI)</td>
<td>Adjusted for: age at study entry, body mass index, county of residence, height, and number of children Also considered: age at birth of first child, daily energy intake, fiber intake, high-density lipoprotein (HDL) cholesterol, ratio of total cholesterol to HDL cholesterol, smoking, total daily fat intake, triglycerides, and &lt;45 versus ≥45 y of age at study entry</td>
</tr>
</tbody>
</table>
### Table 2—continued. Selected results from 11 studies on occupation physical activity and breast cancer risk

<table>
<thead>
<tr>
<th>First author, year (reference No.)</th>
<th>Study design and population</th>
<th>Assessment of physical activity</th>
<th>Measure of association*</th>
<th>Adjustment for confounding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population-based case–control studies</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Coogan, 1997 (50)</td>
<td>Population-based case–control study Western Massachusetts, Maine, New Hampshire, and Wisconsin (USA) 4863 cases diagnosed 1988–1991 6783 control subjects (driver’s license and HCAF) Aged &lt;75 y at reference date 2104 premenopausal case subjects</td>
<td>Self-reported occupation</td>
<td>Physical activity rating (U.S. Department of Labor) Heavy versus sedentary aOR (95% CI) Pre &amp; Post Heavy versus sedentary aOR (95% CI) Pre &amp; Post Heavy versus sedentary aOR (95% CI) Pre &amp; Post</td>
<td>Adjusted for: age, age at first birth, age at menarche, alcohol consumption, benign breast disease, body mass index, education, family history of breast cancer, menopausal status, parity, physical activity during ages 14–22 y, and state of residence Also considered: none</td>
</tr>
<tr>
<td>Dosemeci, 1993 (48)</td>
<td>Hospital-based case–control study Istanbul (Turkey) 241 cases diagnosed 1979–1984 244 controls (other cancers) Unspecified age at reference date †</td>
<td>Self-reported occupational history</td>
<td>Energy expenditure index (kJ/min) Sedentary (&lt;8) versus active (&gt;12) Sitting time index (hours/day) Sedentary (≥6) versus active (&lt;2)</td>
<td>aOR (95% CI) Pre &amp; Post 0.7 (0.2–3.4) P for trend = .23 aOR (95% CI) Pre &amp; Post 1.0 (0.4–2.5) P for trend = .21</td>
</tr>
<tr>
<td>D’Avanzo, 1996 (31)</td>
<td>Hospital-based case–control study Milan, Genoa, Naples, and provinces of Pordenone, Gorizia, Forlì, and Latina (Italy) 2569 cases diagnosed 1991–1994 2588 control subjects (non-cancer conditions) Aged 20–74 y at reference date 988 premenopausal or in menopause case subjects</td>
<td>Self-assessed intensity of work</td>
<td>Age periods</td>
<td>Self-assessed intensity aOR (95% CI) All ages Very tiring versus sitting P for trend &lt; .05 Very tiring versus sitting P for trend &lt; .05 Very tiring versus sitting P for trend &gt; .05 Very tiring versus sitting P for trend &gt; .05 Very tiring versus sitting P for trend &lt; .05 Very tiring versus sitting P for trend &gt; .05</td>
</tr>
</tbody>
</table>

*PMR = proportionate mortality ratio; Pre = premenopausal; Post = postmenopausal; SIR = standardized incidence ratio; SIR<sub>PL</sub> = SIR for physical education teachers; SIR<sub>L</sub> = SIR for language teachers; CI = confidence interval; aRR = relative risk adjusted for confounders listed in last column; aOR = odds ratio adjusted for confounders listed in last column.

†Number of premenopausal cases not available.

‡The studies by Vilhko et al. and Pukkala et al. both use data from the same registry of Finnish teachers.

§The cohort consists of physical education (PE) and language (L) teachers.

¶The studies by Albanes et al. and Steenland et al. both use data from the U.S. National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study.

¶¶Health Care Financing Administration.

Tigations that used job title as a surrogate measure for activity levels assessed usual level from usual occupation (44,50), average level was derived from occupational history (48), baseline levels were assumed from the job held at baseline (47), and recent levels were based on the job held at diagnosis or before retirement (46). Studies based on self-rated physical activity assessed the level for a usual day at baseline (24,49), for the year preceding baseline interview (34), or during specific time periods in life (31). Although the Turkish case–control study (48) assessed lifetime occupational history, no data were presented in relation to physical activity at specific time periods in life. In the Italian case–control study (31), the risk reductions were similar for work-related activity at ages 15–19 years, 30–39 years, and 50–59 years. It is therefore not known during what period of life, if any, work-related physical activity is most protective against breast cancer.
Study findings were inconsistent on whether work-related physical activity decreases the risk of breast cancer among premenopausal and postmenopausal women (31,34,50), among younger women only (47), or among postmenopausal women only (49). Several studies suggest that the reduction in risk activity may be greater among premenopausal women (34,50) or among women less than 60 years of age (31). The Italian case–control study (31), however, reported almost identical risk reductions for premenopausal and postmenopausal women. In contrast, the Framingham Heart Study (24) found no association among a group of primarily postmenopausal women.

Dose–Response Trends

It remains unclear whether breast cancer risk decreases with increasing level of physical activity at work. Three studies (31,34,50) reported statistically significant dose–response trends. Other studies either did not find a significant trend (22,48) or did not statistically assess it (24,46,47,49).

Combined Recreational and Occupational Physical Activities

Although some investigations assessed both recreational and occupational physical activities (22,24,28,31,34,50) as shown in Tables 1 and 2, few used a combined measure when evaluating breast cancer risk. Five cohort studies with a combined measure of activity (24,31,51–53) had inconclusive results. Also, one study (24) considered activities of daily living other than those from leisure-time and occupational sources.

The Italian case–control study (31) found decreased breast cancer risk in relation to leisure-time and occupational physical activities when each was evaluated separately. Although no results were presented, the authors reported that no meaningful information was added by evaluating a combined score. Similarly, a Norwegian follow-up study (52) reported a reduced risk for a combined measure that was not substantially different from that observed for either exercise or occupational activity alone (34). In two prospective cohort studies, the American Cancer Society’s Cancer Prevention Studies I (ACS I) (53) and II (ACS II) (51), women were asked to assess their level of activity as none, slight, moderate, or heavy and to include occupational and nonoccupational sources. In the ACS I cohort (53), the age-adjusted rate ratio, based on 2226 breast cancer case subjects over 13 years of follow-up, was decreased by 16% and was of borderline statistical significance for the highest level of combined activity as compared with the lowest. In the ACS II cohort (51), the corresponding standardized mortality ratio of 123 was based on fewer than five breast cancer deaths and also was not statistically significant. In the Framingham Heart Study (24), physical activities from leisure and occupational sources were measured separately and then combined in a weighted activity score. Although risk was not associated with this combined measure, risk was nonsignificantly increased by 60% in relation to the highest quartile of another combined activity score that included all sources of daily activity (recreational, occupational, and other activities of daily living).

Given these limited but conflicting data, it is unclear whether breast cancer is associated with occupational and recreational activities combined or with activity from all sources of daily living.

Biologic Plausibility

Laboratory studies in rats (5,54,55) support the hypothesis that physical activity may protect against breast cancer, although low levels of exercise have often been found to be more beneficial than higher levels. However, the biologic mechanisms by which physical activity may protect against breast cancer in animals or humans remain unclear.

In epidemiologic studies, associations with menstrual and reproductive characteristics, such as ages at menarche, menopause, and first birth, provide strong evidence that ovarian hormones play an important role in the development of breast cancer (2,56,57). Some investigators (56–58) have proposed that risk is related to cumulative lifetime exposure to cyclic estrogen and perhaps progesterone. Other researchers (19,59,60) have further hypothesized that a woman’s lifetime breast cancer risk is determined by her reproductive behavior up to menopause and that the length of time between menarche and the first birth is the most critical period. These hypotheses would predict that factors that affect a woman’s cumulative exposure to estrogen, or her reproductive pattern, would influence breast cancer risk.

Physical activity has been shown in some studies to influence certain menstrual characteristics, body size (which affects estrogen exposure in postmenopausal women), and levels of hormones in serum. It is therefore plausible that physical activity reduces breast cancer risk through hormone-related pathways (15,61,62), although other pathways, such as effects on the immune system, may also be important (7,10,16).

We review the evidence on the biologic plausibility of an association between breast cancer and physical activity to determine whether this information can aid in predicting a decrease among subgroups of women, an optimal time period during which the exercise should be performed, or the frequency, duration, or intensity of physical activity necessary to reduce breast cancer risk. Ultimately, such information should enhance the development of questionnaires used to assess physical activity in epidemiologic studies.

Menstrual Characteristics

Effects of occupational physical activity on menstrual function are largely unexplored (63). Recreational exercise, however, has been associated with various changes in menstrual characteristics (64). The onset of menstruation is delayed in girls participating in intensive athletic training, such as running, swimming, and ballet dancing (65–67), or competitive school sports (68). Although age at menarche was not associated with energy expenditure and duration of time spent in noncompetitive sports activities in a prospective study of school girls (68), another study among girls 8–15 years of age (69) found a statistically significant trend with duration of sports activities. Thus, physical activity that is moderate in intensity and duration may also delay age at menarche. The influence of physical activity on age at menarche could operate through an effect on body weight or body fat, both of which are determinants of the onset of menstruation (67,70).
Little is known about the relation between physical activity and age at menopause (71). One retrospective cohort study (20) found a younger age at natural menopause among former college athletes. However, in a prospective study (72), adult physical activity was not more common among women with an earlier age at menopause.

Other changes in menstrual characteristics associated with athletic training among adolescents and young adults include secondary amenorrhea, anovulation, and luteal phase deficiencies (63,73,74). Anovulatory, irregular, long, or short cycles are also more frequent among moderately active women than among inactive women (15,63,75). Disturbances in menstrual function may even be present in athletes with apparently normal menstrual cycles (76,77). Later onset of regular ovulatory cycles and lower concentrations of estrogen in serum are also associated with late age at menarche (78).

The cumulative exposure to estrogen model (discussed above) (58) predicts that amenorrhea, anovulation, and progesterone deficiency will reduce breast cancer risk by reducing a woman’s lifetime exposure to estrogen. However, unlike age at menarche or menopause, no clear associations between breast cancer risk and these menstrual cycle characteristics have been found in epidemiologic studies [reviewed in (2)]. Measurement of menstrual cycle characteristics in epidemiologic studies is much more difficult than assessment of ages at menarche and menopause.

It appears that, if physical activity affects breast cancer risk through changes in menstrual characteristics, several alternative activity patterns may be optimal for risk reduction. If exercise affects risk by delaying age at menarche, then preadolescent or adolescent activity (either vigorous or moderate in intensity) would be most important. If physical activity operates through inducing an earlier age at menopause or through alterations in menstrual cycle characteristics such as amenorrhea or anovulation, then energy expenditure throughout the premenopausal period may also be important. If the critical time of exposure for breast cancer is between the ages at menarche and first birth (19,60), then exercise during that period may be the most crucial.

**Body Size**

In epidemiologic studies, increasing levels of body size, as measured by the body mass index, have been positively associated with increasing breast cancer risk among postmenopausal women (2), although findings are inconsistent in cohort studies (79,80). In addition, heavier women may have a decreased risk for developing premenopausal breast cancer (79,80). Furthermore, it appears as though weight gain in the adult years is related to an elevated risk of postmenopausal breast cancer; however, it is unclear whether there is a corresponding reduction in risk with weight loss (79). Thus, it is plausible that physical activity could reduce breast cancer risk by preventing weight gain or perhaps inducing weight loss.

Obesity is a major determinant of circulating estrone and estradiol concentrations in postmenopausal women (81). With depressed levels of sex hormone-binding globulin, higher levels of free estradiol and free testosterone have been found in obese women (81,82). Physical activity has been associated with a lower body mass index (83) and may also reduce weight and fat stores (84,85). Massive weight loss, however, is required to lower free estradiol levels in obese women (82), yet weight loss through exercise in already obese women is difficult (83). It is possible that physical activity may be more useful as a preventive measure against breast cancer by reducing the likelihood of weight gain, particularly among postmenopausal women. At least one study (86) has reported that participation in vigorous levels of exercise training, three to five times a week, by older women may not induce a substantial reduction in weight but can favorably shift the balance from body fat to lean tissue. Thus, exercise throughout the postmenopausal years may be important in lowering breast cancer risk.

In premenopausal women, obesity is associated with amenorrhea, low progesterone concentrations, and irregular menstrual periods (56). These characteristics of obesity may help prevent premenopausal breast cancer under the estrogen-plus-progestogen theory of breast cancer development promulgated by Pike et al. (58); this theory predicts that low levels of these hormones reduce breast cancer risk.

**Serum Hormone Levels**

Many studies have demonstrated that physical activity alters the hormonal milieu in premenopausal women, presumably by increasing the levels of catecholamine and β-endorphin, both of which inhibit the hypothalamic secretion of gonadotropin-releasing hormone; decreased synthesis and secretion of follicle-stimulating hormone and luteinizing hormone in turn decrease the production and secretion of estrogen and progesterone (74), thereby decreasing exposure to estrogen and progesterone. Studies of athletes have reported altered patterns of pulsatile secretion of luteinizing hormone (76,87) and lower concentrations of follicle-stimulating hormone (88,89), estrogen (89–94), and progesterone (89,90,95,96).

In postmenopausal women, moderate levels of physical activity, as compared with little or none, have been associated with lower concentrations of circulating estrogen (97,98), although the evidence has been inconsistent (99). Although past case-control and cohort studies have been unable to show a clear association between serum hormone levels and breast cancer risk among premenopausal or postmenopausal women [reviewed in (57)], several recent cohort studies (100,101) have reported statistically significant associations between levels of endogenous estrogens and androgens and risk of postmenopausal breast cancer.

**Effect on Immune Function**

The immune system, which is involved in regulating one’s susceptibility to both the initiation and promotion of tumors, can be suppressed or enhanced by physical activity (102), suggesting that perhaps persistent exercise is most optimal for reducing cancer risk. Changes in the immune system are dependent on the intensity, duration, and frequency of activity. Currently, it is unclear which alterations will result in either detrimental or protective effects. In general, immune function is compromised by extreme levels of activity, high more so than low, and is at an optimal level during moderate exercise (103,104). The evidence, albeit limited, of improved immune function indicates that macrophages, natural killer cells, lymphokine-
activated killer cells and their regulating cytokines, neutrophils,
and acute-phase proteins increase in number and/or activity in
response to exercise (102). As a result, the immune system’s
ability to slow the growth rate and to lyse tumor cells is en-
hanced (102). These more favorable changes to immune func-
tion are generally associated with low to moderate levels of
activity (102).

High-intensity activities result in immunosuppression, as evi-
denced by both a reduction in leukocytosis and an impaired
functioning of immune system cells (105). A proposed unifying
mechanism for this immune depression involves the reduced
production of glutamine by the skeletal muscles during exercise
(105). Glutamine metabolism provides essential fuel for the cells
of the immune system in response to an immune challenge (105).

Another hypothesis holds that exercise places the body under
oxidative stress, which renders it more vulnerable to cell and
tissue damage as a result of oxidation and peroxidation of lipids,
proteins, and DNA by free radicals (102,106,107). Production of
free radicals and other byproducts that can be converted into free
radicals increases during exercise-associated aerobic metabo-
liston (106,107). Simultaneously, a rise in antioxidant enzymes
occurs, and these enzymes are capable of converting free radi-
cals to a less harmful state (106,107). Uncertainties about the
free radical–antioxidant relationship include the extent to which
antioxidants and free radicals associated with physical activity
counterbalance one another. In addition, it is currently unknown
whether this relationship varies for different types of exercise
and whether antioxidants from diet or supplementation are ef-
fective in fighting free radicals produced by physical activity
(106,107).

Summary and Recommendations

Epidemiologic studies have repeatedly observed a reduced
risk of breast cancer in relation to increased levels of physical
activity. Exercise appears to decrease risk among premenopausal
and postmenopausal women, but it is unclear whether a reduc-
tion in risk in relation to occupational activity applies to all
women. Data are too sparse to assess the combined effect of
recreational and occupational activities. The inverse association
with exercise is more consistently reported in case–control stud-
ies than in cohort studies, suggesting that recall bias may be an
explanation for these observations. Physical activity has been
hypothesized to affect breast cancer through changes in men-
strual characteristics, body size, serum hormone levels, or im-
mune function, suggesting alternative time periods during which
the exercise is performed that may be important for reducing
risk. Epidemiologic studies are inconsistent on whether the tim-
ing, intensity, or frequency of physical activity is critical for
decreasing risk. Difficulties in accurately assessing physical ac-
tivity, including whether there is a dose–response relationship,
undoubtedly contribute to these observed inconsistencies. Al-
though, as results from animal studies suggest, it is possible that
there is a threshold and breast cancer risk does not further de-
crease with increasing levels of activity.

Future epidemiologic research should focus on the following:
using either a prospective or a retrospective cohort design to rule
out recall bias as an explanation for the observed decrease in
breast cancer risk; improving the reliability and validity of the
methods required for complete assessment of the various com-
ponents that define physical activity for use in both cohort and
case–control studies to clarify whether there is a dose–response
relation and to identify the optimal frequency, duration, and
intensity of the physical activity needed to decrease risk; meas-
suring lifetime levels of recreational exercise and occupational
activity to identify the critical time periods, if any, during which
women or girls should be more physically active; including mea-
sures of physical activity during the follow-up period of cohort
studies to account for changes in exposure; improving quantifi-
cation of physical activity from all sources, including recreation,
occupation, and daily living; exploring the potential interactive
roles of physical activity, nutrition, and body size on breast
cancer development; and collaborating with scientists in other
disciplines to elucidate the biologic mechanisms through which
physical activity may reduce breast cancer risk.

References

(2) Kelsey JL, Bernstein L. Epidemiology and prevention of breast cancer.
(3) Brinton LA. Ways that women may possibly reduce their risk of breast

(4) Gammon MD, Britton JB, Teitelbaum SL. Does physical activity reduce
the risk of breast cancer? Review of the epidemiologic evidence. Meno-
(5) Shephard RJ. Exercise and cancer: linkages with obesity? Crit Rev Food
(6) Sternfeld B. Cancer and the protective effect of physical activity: the
413–20.
(8) Kohl HW, LaPorte RE, Blair SN. Physical activity and cancer. An epi-
(10) Kramer MM, Wells CL. Does physical activity reduce risk of estrogen-
(11) Francis K. Physical activity: breast and reproductive cancer. Compr Ther
(12) Friedenreich CM, Rohan TE. A review of physical activity and breast
(13) Hoffman-Goetz L, Husted J. Exercise and breast cancer: review and criti-
(14) Gammon MD, John EM. Recent etiologic hypotheses concerning breast
(15) Bernstein L, Ross RK, Lobo RA, Hanisch R, Kralio MD, Henderson BE.
The effects of moderate physical activity on menstrual cycle patterns in
(16) McTiernan A. Exercise and breast cancer—time to get moving? [editori-
(17) LaPorte RE, Montoye HJ, Caspersen CJ. Assessment of physical activity
in epidemiologic research: problems and prospects. Public Health Rep
1985;100:131–46.
(18) McArdle WD, Katch FI, Katch VL. Exercise physiology: energy, nutri-
(19) Colditz GA. Fat, estrogens, and the time frame for prevention of breast
(20) Frisch RE, Wyshak G, Albright NL, Albright TE, Schiff I, Witschi J, et
al. Lower lifetime occurrence of breast cancer and cancers of the repro-
ductive system among former college athletes. Am J Clin Nutr 1987;45(5
Suppl):328–35.
(21) Paffenbarger RS Jr, Hyde RT, Wing AL. Physical activity and incidence

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REVIEW 115


Note

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