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. [J Natl Cancer Inst 1998;90:100–17]

Approximately 180 200 women in the United States will be newly diagnosed with breast cancer, and some 44 190 will die of their disease in 1997 *(1)*. Although early detection by mammography reduces breast cancer mortality, there are no proven strategies to prevent development of the disease *(2,3)*. Efforts directed toward the prevention of breast cancer are frustrated by the lack of established risk factors that are easily modified to reduce risk *(4)*. Physical activity is a promising preventive measure for many chronic diseases, including cancer *(5–9)*. Previous reviews *(4,9–14)* have concluded that evidence is suggestive of a decreased risk of breast cancer in relation to recreational exercise, but the data were scant and controversial.

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

**Affiliations of authors:* M. D. Gammon, J. A. Britton, Columbia University School of Public Health, Division of Epidemiology, New York, NY; E. M. John, Northern California Cancer Center, Union City.

Correspondence to: Marilie D. Gammon, Ph.D., Columbia University School of Public Health, Division of Epidemiology, 622 West 168th St., PH18–107, New York, NY 10032.

See ''Note'' following ''References.''

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 five cohort studies that followed are conflicting. One recent prospective cohort study by Thune et al. *(34)* also reported a statistically significant decrease in risk of 37% among 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

First author, year (reference No.)	Study design and population	Assessment of physical activity	Measure of association*			
			Timing	Estimate of effect by menopausal status or age		Adjustment for confounding
Retrospective cohort studies						
Frisch 1987 *(20)*	Retrospective cohort study U.S. colleges (USA) 5398 living alumnae who graduated between 1925 and 1981 Follow-up 1925–1981 69 prevalent cases†	Participation in sports from college records	College	Participation in sports Non-athlete versus athlete	aRR (95% CI) Pre & Post 1.86 (1.00—3.47)	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
Paffenbarger, 1987 *(21)*	Retrospective cohort study University of Pennsylvania (USA) 4706 women who graduated between 1916 and 1950 Follow-up 1916–1978 62 incident cases†	Participation in sports from college records	College	Hours/week ≥5 versus <5	aRR (*P*) Pre & Post 0.96 (.92)	Adjusted for: age and year of birth Also considered: none
Prospective cohort studies						
Albanes, 1989 *(22)*	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	Self-assessment score	Usual day at baseline	Self-assessment score None/little versus much None/little versus much None/little versus much	aRR (95% CI) Pre & 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)	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
Paffenbarger, 1992 *(23)*	Prospective cohort study University of Pennsylvania (USA) 2370 alumnae aged 40–50 y at baseline in 1962 Follow-up 1962–1977 73 incident cases†	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 <1000	aRR (95% CI) Pre & Post 0.88 (0.54–1.43)	Adjusted for: age, body mass index, and history of maternal cancer Also considered: none

Table 1—continued. Selected results from 16 studies on recreational physical activity and breast cancer risk

First author, year (reference No.)	Study design and population	Assessment of physical activity	Measure of association*			
			Timing	Estimate of effect by menopausal status or age		Adjustment for confounding
Dorgan, 1994 *(24)*	Prospective cohort study Framingham Heart study (USA) 2298 women aged 35–68 y at fourth examination in 1954–1956 Follow-up 1954–1984 117 incident cases 5 premenopausal case subjects	Self-reported hours spent at sleep/rest, sedentary/ slight, and moderate/heavy activities	Usual day at baseline	One hour spent at Moderate/heavy versus sleep/rest	aRR (95% CI) Pre & Post 1.2 (1.0–1.6) Post Not available; estimates similar to combined groups	Adjusted for: age, age at first pregnancy, alcohol consumption, education, menopausal status, number of live births, and occupation Also considered: body mass index, height, postmenopausal exogenous hormone use, and weight
Thune, 1997 *(34)*	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	Self-assessment score	Year preceding baseline interview	Self-assessment score Regular versus sedentary Regular versus sedentary Regular versus sedentary	aRR (95% CI) Pre & Post 0.63 (0.42–0.95) *P* for trend = .04 Pre 0.53 (0.25–1.14) *P* for trend = .10 Post 0.67 (0.41–1.10) *P* for trend = .15	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 <45 versus ⩾45 years of age at study entry
Population-based case–control studies						
Bernstein, 1994 *(25)*	Population-based case–control study Los Angeles County (USA) 545 cases diagnosed 1983–1989 545 control subjects (neighborhood) Aged ⩽40 y at reference date Presumably all women premenopausal since ⩽40 y	Self-reported name, hours/week, and start and stop ages of activities	Time period Within 10 y after menarche Lifetime history	Hours/week ⩾5.6 versus none ⩾3.8 versus none	aOR (95% CI) Pre 0.70 (0.47–1.06) *P* for trend = .027 0.42 (0.27–0.64) *P* for trend = .0001	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 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

Table 1—continued. Selected results from 16 studies on recreational physical activity and breast cancer risk

First author, year (reference No.)	Study design and population	Assessment of physical activity	Measure of association*			
			Timing	Estimate of effect by menopausal status or age		Adjustment for confounding
Friedenreich, 1995 *(26)*	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	Self-reported hours/week participating in light, moderate, and vigorous activities separately for summer and winter activities	Year prior to diagnosis	Kilocalories/week >4000 versus 0 >4000 versus 0 >4000 versus 0	aOR (95% CI) Pre & 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	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
Mittendorf, 1995 *(28)*	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 <75 y at reference date 31% of women premenopausal	Self-reported name and frequency of ⩽3 strenuous physical activities or team sports	Ages 14–22 y	Frequency of strenuous activity/year ⩾364 versus none	aOR (95% CI) Pre & Post 0.5 (0.4–0.7) *P* for trend = .02 Post not available; estimates similar to combined groups	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
McTiernan, 1996 *(30)*	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	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	Age periods Adolescence (12–21 y) Adulthood (activity that extended into 2 y before reference date)	Hours/week >3.0 versus none >5.0 versus none >5.0 versus none	aOR (95% CI) Pre & 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	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 1—continued. Selected results from 16 studies on recreational physical activity and breast cancer risk

First author, year (reference No.)	Study design and population	Assessment of physical activity	Measure of association*			
			Timing	Estimate of effect by menopausal status or age		Adjustment for confounding
Chen, 1997 *(33)*	Population-based case–control study Three-county Seattle Metropolitan Area (USA) 747 cases diagnosed 1983–1990 961 control subjects (RDD‖) Aged 21–45 y at reference date 643 premenopausal case subjects	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 (>2/mo in any year)	Age periods Ages 12–21 y Adulthood (2-y period before reference date)	Hours/week ≥4 versus 0 ≥4 versus 0	aOR (95% CI) Pre & Post 1.21 (0.80–1.82) *P* for trend = .51 0.92 (0.69–1.23) *P* for trend = .97	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
Gammon, 1998 *(35)*	Population-based case–control study Atlanta, Seattle, New Jersey (USA) 1647 cases diagnosed 1990–1992 1501 control subjects (RDD‖) Aged <45 y at reference date 1474 premenopausal case subjects	Self-reported frequency per week or month of moderate and vigorous activities; participation in sports to keep weight low	Age periods 12–13 y 20 y Past year (year before interview) Average of 3 time periods	Relative units/week ≥75.01 versus ≤24.81 ≥35.01 versus ≤4.73 ≥35.01 versus ≤3.35 ≥42.96 versus ≤18.07	aOR (95% CI) Pre & Post 0.99 (0.79–1.24) *P* for trend = .33 1.10 (0.88–1.38) *P* for trend = .08 1.09 (0.87–1.37) *P* for trend = .13 1.01 (0.81–1.25) *P* for trend = .42	Adjusted for: adult body mass index, age at first birth, age at menarche, age, body mass index at age 20, caloric intake in past year, center, education, family income, family history of breast cancer, history of breast biopsy, lactation, marital status, use of menopausal estrogens, menopausal status, number of abortions, number of miscarriages, oral contraceptive use, parity, race, smoking, and usual alcohol consumption Also considered: chemotherapy, frequency of breast self-examinations and mammography, interval of time between interview and reference date, and stage
Hospital-based case–control studies						
Taioli, 1995 *(27)*	Hospital-based case–control study Geographic location not available 617 cases diagnosed 1987–1990 531 control subjects (non-tobacco- or alcohol-related diseases) All ages at reference date 196 premenopausal case subjects	Self-reported name, frequency (months/year and number of years), and duration per episode of ≤2 activities from a list of 26 activities	Ages 15–22 y	Hours/week ≥3 versus non-exerciser ≥3 versus non-exerciser	aOR (95% CI) Pre 0.7 (0.4–1.4) Post 1.0 (0.6–1.8)	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

Table 1—continued. Selected results from 16 studies on recreational physical activity and breast cancer risk

First author, year (reference No.)	Study design and population	Assessment of physical activity	Measure of association*			
			Timing	Estimate of effect by menopausal status or age		Adjustment for confounding
Hirose, 1995 *(29)*	Hospital-based case–control study Nagoya (Japan) 1186 cases diagnosed 1988–1992 23 163 control subjects (non-cancer conditions) Aged 18+ y at reference date 607 premenopausal case subjects	Participation in exercise for health	Not specified	Times/week ⩾2 versus none ⩾2 versus none	aOR (95% CI) Pre 0.74 (0.55–0.99) Post 0.72 (0.53–0.97)	Adjusted for: age and first year visit 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
D'Avanzo, 1996 *(31)*	Hospital-based case–control study Milan, Genoa, Naples, and provinces of Pordenone, Gorizia, Forli, Latina (Italy) 2569 cases diagnosed 1991–1994 2588 control subjects (non-cancer conditions) Aged 20–74 y at reference date 988 premenopausal or perimenopausal case subjects	Self-reported duration of leisure time activity in predefined categories: <2, 2–4, 5–7, 7+ hours/week	Age periods 15–19 y 30–39 y 50–59 y	Hours/week >7 versus <2 >7 versus <2 >7 versus <2	aOR (95% CI) Pre & Post 0.94 (0.77–1.16) *P* for trend ⩾.05 0.77 (0.56–1.06) *P* for trend <.05 0.68 (0.40–1.09) *P* for trend ⩾.05	Adjusted for: age, age at first birth, age at menarche, age at menopause, calorie intake, center, education, history of breast cancer in first-degree relatives, menopausal status, number of births, and previous benign breast disease Also considered: body mass index and menstrual cycle

Table 1—continued. Selected results from 16 studies on recreational physical activity and breast cancer risk

First author, year (reference No.)	Study design and population	Assessment of physical activity	Measure of association*			
			Timing	Estimate of effect by menopausal status or age		Adjustment for confounding
Hu, 1997 *(32)*	Hospital-based case–control study Gifu (Japan) 157 cases diagnosed 1989–1993 369 control subjects (screened for breast cancer) Aged 25–65+ y at screening 87 premenopausal case subjects	Self-reported total hours/week in moderate and strenuous activities	Age periods	Kilocalories/week	aOR (95% CI) Pre	Adjusted for: age, age at menarche, age at first birth, body mass index 4 y before study, duration of breast feeding, number of births, and residential area Also considered: active smoking, age at menopause, drinking status, height, husband's smoking, number of pregnancies, relative height and weight at 12 y of age, and weight
			Teenage years	⩾1100 versus 0	0.74 (0.38–1.38) *P* for trend = .294	
			Twenties	⩾650 versus 0	1.01 (0.54–1.87) *P* for trend = .876	
					Post	
			Teenage years	⩾700 versus 0	1.39 (0.61–3.13) *P* for trend = .338	
			Twenties	⩾1100 versus 0	0.53 (0.19–1.52) *P* for trend = .973	

*aRR = relative risk adjusted for confounders listed in last column; CI = confidence interval; Pre = premenopausal; Post = postmenopausal; aOR = odds ratio adjusted for confounders listed in last column.

†Number of premenopausal case subjects not available.

‡U.S. National Health and Nutrition Examination Survey.

§Health Care Financing Administration.

‖Random-digit dialing.

effect and may have contributed to their inconsistent findings, particularly with regard to identification of subgroups of women who may be at high risk. The generally larger numbers of case subjects who participated in case–control studies may have helped produce the more consistent results.

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.

Physical Activity Assessment

Misclassification. Inconclusive findings in the cohort studies may be due to inadequate assessment of exercise at baseline or failure to account for any change in exercise since the baseline assessment. Often the cohort studies relied on self-report of exercise at a single point in time, such as a day at baseline *(22–24)* or the year preceding baseline *(34)*, or derived exercise from college records *(20)*, possibly leading to masking of any true effect.

Case–control studies usually require a single contact with each study participant, which facilitates the use of a more comprehensive questionnaire to assess the frequency, duration, and intensity of physical activity at multiple time periods during life. However, of primary concern in case–control studies is the possibility of recall bias, in which case subjects, because of the seriousness of their diagnosis, are more motivated to recall past events than control subjects, thereby causing spurious associations. For a spurious inverse association, physical activity would have to be overreported by control subjects or underreported by case subjects. Because physical activity has been widely promulgated as a preventive measure for heart disease, for example, it is possible that, to appear socially acceptable, control subjects overestimated their participation in recreational activities to a

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 life. The inves-

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

First author, year (reference No.)	Study design and population	Assessment of physical activity	Measure of association*			
			Timing	Estimate of effect by menopausal status or age		Adjustment for confounding
Record-based studies						
Vena, 1987 *(44)*	Proportionate mortality study Washington State (USA) 25 000 women of all ages at death 1974–1979 791 deaths†	Occupation listed on death certificate	Usual occupation	Physical activity rating (U.S. Department of Labor) 1 (low) 2 3–5 (high)	PMR (*P*) Pre & Post 115 (<.05) 83 (<.01) 85 (<.05)	Adjusted for: none Also considered: none
Zheng, 1993 *(46)*	Linkage study Shanghai (China) 1982 census population 2736 case subjects aged 30+ y at diagnosis in 1980–1984†	Self-reported occupation	At diagnosis or before retirement	Energy expenditure index (kJ/min) Low (<8) Medium (8–12) High (>12) Sitting time index (working hours) Long (>80%) Moderate (20%–80%) Short (<20%)	SIR (*P*) Pre & Post 131 (<.01) 95 (>.05) 79 (<.01) SIR (*P*) Pre & Post 127 (<.01) 110 (<.01) 93 (<.05)	Adjusted for: none Also considered: none
Retrospective 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 PE versus population L versus population Ratio SIR_{PE}/SIR_L	SIR (95% CI) [1]20+ y 1.28 (≥.05) 1.59 (<.001) 0.81 (≥.05)	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
[2]Pukkala,‡ 1993 *(47)*	PE§ teachers alive in 1959 and 1973 L§ teachers alive in 1954 and 1967 Compared with national incidence of female breast cancer Follow-up 1967–1987 [1]924 PE§ and 3239 L§ teachers 128 incident cases 45 case subjects aged 26–49 y at diagnosis Follow-up 1967–1991 [2]1499 PE§ and 8619 L§ teachers 228 incident cases 82 case subjects aged 20–49 y at diagnosis				[1]20–49 y 0.93 (≥.05) 1.51 (<.05) 0.62 (≥.05) [1]50+ y 1.44 (≥.05) 1.64 (<.001) 0.88 (≥.05) [2]20+ y 1.35 (0.95–1.87) 1.48 (1.27–1.69) 0.89 [2]20–49 y 1.01 (0.46–1.91) 1.38 (1.08–1.74) 0.73 [2]50+ y 1.52 (1.00–2.21) 1.54 (1.28–1.83) 0.99	

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

First author, year (reference No.)	Study design and population	Assessment of physical activity	Measure of association*			
			Timing	Estimate of effect by menopausal status or age		Adjustment for confounding
Prospective cohort studies						
[3]Albanes,‖ 1989 *(22)* [4]Steenland,‖ 1995 *(49)*	Prospective cohort study NHANES I Epidemiologic Follow-up Study (USA) 7413 women aged 25–74 y at baseline, 1971–1975 [3]Follow-up 1971–1984 122 incident cases 46 premenopausal case subjects	[3,4]Self-assessed intensity	[3,4]Usual day at baseline	Self-assessed intensity Inactive versus very active Inactive versus very active Inactive versus very active	aRR (95% CI) [3]Pre & Post 1.1 (0.6–2.0) [3]Pre 0.4 (0.1–1.8) [3]Post 1.5 (0.7–2.8)	[3]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 prior to diagnosis of breast cancer, and parity
	[4]Follow-up 1971–1987 163 incident cases†			Little versus a lot Little versus a lot	[4]Pre & Post 0.86 (0.61–1.20) [4]Post 1.5 (1.08–2.08)	[4]Adjusted for: age, alcohol consumption, body mass index, cholesterol, diabetes, income, menopausal status, race, recreational physical activity, pulse, and smoking Also considered: none
Dorgan, 1994 *(24)*	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	Self-reported hours spent at sleeping and sedentary, slight, moderate, and heavy activities during workdays	Usual day at baseline	One hour spent at Moderate/heavy versus sleep/rest	aRR (95% CI) Pre & Post 1.1 (0.9–1.3)	Adjusted for: age, age at first pregnancy, alcohol consumption, education, menopausal status, number of live births, and occupation Also considered: body mass index, height, postmenopausal exogenous hormone use, and weight
Thune, 1997 *(34)*	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	Self-assessed intensity of work	Year preceding baseline interview	Self-assessed intensity Heavy labor versus sedentary Lifting/heavy versus sedentary Lifting/heavy versus sedentary	aRR (95% CI) Pre & Post 0.48 (0.25–0.92) *P* for trend = .02 Pre 0.48 (0.24–0.95) *P* for trend = .03 Post 0.78 (0.52–1.18) *P* for trend = .24	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 <45 versus ⩾45 y of age at study entry

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

First author, year (reference No.)	Study design and population	Assessment of physical activity	Measure of association*			
			Timing	Estimate of effect by menopausal status or age		Adjustment for confounding
Population-based case–control studies						
Coogan, 1997 *(50)*	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 HCFA¶) Aged <75 y at reference date 2104 premenopausal case subjects	Self-reported occupation	Usual occupation	Physical activity rating (U.S. Department of Labor) Heavy versus sedentary Heavy versus sedentary Heavy versus sedentary	aOR (95% CI) Pre & Post 0.82 (0.63–1.08) *P* for trend = .007 Pre 0.64 (0.32–1.28) *P* for trend = .16 Post 0.87 (0.64–1.18) *P* for trend = .04	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
Hospital-based case–control studies						
Dosemeci, 1993 *(48)*	Hospital-based case–control study Istanbul (Turkey) 241 cases diagnosed 1979–1984 244 controls (other cancers) Unspecified age at reference date†	Self-reported occupational history	Lifetime history	Energy expenditure index (kJ/min) Sedentary (<8) versus active (>12) Sitting time index (hours/day) Sedentary (>6) versus active (<2)	aOR (95% CI) Pre & Post 0.7 (0.2–3.4) *P* for trend = .23 aOR (95% CI) Pre & Post 1.0 (0.4–2.5) *P* for trend = .21	Adjusted for: age, smoking, and socioeconomic status Also considered: none
D'Avanzo, 1996 *(31)*	Hospital-based case–control study Milan, Genoa, Naples, and provinces of Pordenone, Gorizia, Forli, 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	Self-assessed intensity of work	Age periods 15–19 y 30–39 y 50–59 y 30–39 y 30–39 y 30–39 y	Self-assessed intensity Very tiring versus sitting Very tiring versus sitting Very tiring versus sitting Very tiring/tiring versus sitting Very tiring/tiring versus sitting Very tiring/tiring versus sitting	aOR (95% CI) All ages 0.64 (0.37–1.11) *P* for trend <.05 0.54 (0.33–0.89) *P* for trend <.05 0.62 (0.30–1.25) *P* for trend ⩾.05 20–49 y 0.59 (0.4–0.9) *P* for trend <.05 50–59 years 0.55 (0.3–0.9) *P* for trend <.05 60–74 y 0.79 (0.5–1.2) *P* for trend ⩾.05	Adjusted for: age, age at first birth, age at menarche, age at menopause, calorie intake, center, history of breast cancer in first-degree relatives, menopausal status, number of births, and previous benign breat disease Also considered: body mass index, education, and menstrual cycle

*PMR = proportionate mortality ratio; Pre = premenopausal; Post = postmenopausal; SIR = standardized incidence ratio; SIR_{PE} = SIR for physical education teachers; SIR_L = 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 Vihko 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.

Subgroup Analyses

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 to 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 *(85).* 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 enhanced *(102)*. These more favorable changes to immune function are generally associated with low to moderate levels of activity *(102)*.

High-intensity activities result in immunosuppression, as evidenced 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 metabolism *(106,107)*. Simultaneously, a rise in antioxidant enzymes occurs, and these enzymes are capable of converting free radicals 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 effective 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 reduction 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 studies 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 menstrual characteristics, body size, serum hormone levels, or immune 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 timing, intensity, or frequency of physical activity is critical for decreasing risk. Difficulties in accurately assessing physical activity, including whether there is a dose–response relationship, undoubtedly contribute to these observed inconsistencies. Although, as results from animal studies suggest, it is possible that there is a threshold and breast cancer risk does not further decrease 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 components 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; measuring 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 measures of physical activity during the follow-up period of cohort studies to account for changes in exposure; improving quantification 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

(1) Anonymous. Cancer facts and figures—1997. Atlanta (GA): American Cancer Society, 1997.

(2) Kelsey JL, Bernstein L. Epidemiology and prevention of breast cancer. Annu Rev Public Health 1996;17:47–67.

(3) Brinton LA. Ways that women may possibly reduce their risk of breast cancer [editorial]. J Natl Cancer Inst 1994;86:1371–2.

(4) Gammon MD, Britton JB, Teitelbaum SL. Does physical activity reduce the risk of breast cancer? Review of the epidemiologic evidence. Menopause 1996;3:172–80.

(5) Shephard RJ. Exercise and cancer: linkages with obesity? Crit Rev Food Sci Nutr 1996;36:321–39.

(6) Sternfeld B. Cancer and the protective effect of physical activity: the epidemiological evidence. Med Sci Sports Exerc 1992;24:1195–209.

(7) Shephard RJ. Physical activity and cancer. Int J Sports Med 1990;11: 413–20.

(8) Kohl HW, LaPorte RE, Blair SN. Physical activity and cancer. An epidemiological perspective. Sports Med 1988;6:222–37.

(9) Anonymous. Physical activity and health: a report of the Surgeon General. Washington (DC): US Department of Health and Human Services, 1997.

(10) Kramer MM, Wells CL. Does physical activity reduce risk of estrogen-dependent cancer in women? Med Sci Sports Exerc 1996;28:322–34.

(11) Francis K. Physical activity: breast and reproductive cancer. Compr Ther 1996;22:94–9.

(12) Friedenreich CM, Rohan TE. A review of physical activity and breast cancer. Epidemiology 1995;6:311–7.

(13) Hoffman-Goetz L, Husted J. Exercise and breast cancer: review and critical analysis of the literature. Can J Appl Physiol 1994;19:237–52.

(14) Gammon MD, John EM. Recent etiologic hypotheses concerning breast cancer. Epidemiol Rev 1993;15:163–8.

(15) Bernstein L, Ross RK, Lobo RA, Hanisch R, Krailo MD, Henderson BE. The effects of moderate physical activity on menstrual cycle patterns in adolescence: implications for breast cancer prevention. Br J Cancer 1987; 55:681–5.

(16) McTiernan A. Exercise and breast cancer—time to get moving? [editorial]. N Engl J Med 1997;336:1311–2.

(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, nutrition, and human performance. Malvern (PA): Lea & Febiger, 1991.

(19) Colditz GA. Fat, estrogens, and the time frame for prevention of breast cancer [editorial]. Epidemiology 1995;6:209–11.

(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 reproductive system among former college athletes. Am J Clin Nutr 1987;45(1 Suppl):328–35.

(21) Paffenbarger RS Jr, Hyde RT, Wing AL. Physical activity and incidence

of cancer in diverse populations: a preliminary report. Am J Clin Nutr 1987;45(1 Suppl):312–7.
(22) Albanes D, Blair A, Taylor PR. Physical activity and risk of cancer in the NHANES I population. Am J Public Health 1989;79:744–50.
(23) Paffenbarger RS Jr, Lee IM, Wing AL. The influence of physical activity on the incidence of site-specific cancers in college alumni. In: Jacobs MM, editor. Exercise, calories, fat, and cancer. New York: Plenum Press, 1992:7–15.
(24) Dorgan JF, Brown C, Barrett M, Splansky GL, Kreger BE, D'Agostino RB, et al. Physical activity and risk of breast cancer in the Framingham Heart Study. Am J Epidemiol 1994;139:662–9.
(25) Bernstein L, Henderson BE, Hanisch R, Sullivan-Halley J, Ross RK. Physical exercise and reduced risk of breast cancer in young women. J Natl Cancer Inst 1994;86:1403–8.
(26) Friedenreich CM, Rohan TE. Physical activity and risk of breast cancer. Eur J Cancer Prev 1995;4:145–51.
(27) Taioli E, Barone J, Wynder EL. A case–control study on breast cancer and body mass. The American Health Foundation—Division of Epidemiology. Eur J Cancer 1995;31A:723–8.
(28) Mittendorf R, Longnecker MP, Newcomb PA, Dietz AT, Greenberg ER, Bogdan GF, et al. Strenuous physical activity in young adulthood and risk of breast cancer (United States). Cancer Causes Control 1995;6:347–53.
(29) Hirose K, Tajima K, Hamajima N, Inoue M, Takezaki T, Kuroishi T, et al. A large-scale, hospital-based case–control study of risk factors of breast cancer according to menopausal status. Jpn J Cancer Res 1995;86: 146–54.
(30) McTiernan A, Stanford JL, Weiss NS, Daling JR, Voigt LF. Occurrence of breast cancer in relation to recreational exercise in women age 50–64 years. Epidemiology 1996;7:598–604.
(31) D'Avanzo B, Nanni O, La Vecchia C, Franceschi S, Negri E, Giacosa A, et al. Physical activity and breast cancer risk. Cancer Epidemiol Biomarkers Prev 1996;5:155–60.
(32) Hu YH, Nagata C, Shimizu H, Kaneda N, Kashiki Y. Association of body mass index, physical activity, and reproductive histories with breast cancer: a case–control study in Gifu, Japan. Breast Cancer Res Treat 1997; 43:65–72.
(33) Chen CL, White E, Malone KE, Daling JR. Leisure-time physical activity in relation to breast cancer among young women (Washington, United States). Cancer Causes Control 1997;8:77–84.
(34) Thune I, Brenn T, Lund E, Gaard M. Physical activity and the risk of breast cancer. N Engl J Med 1997;336:1269–75.
(35) Gammon MD, Schoenberg JB, Britton JA, Kelsey JL, Coates RJ, Brogan D, et al. Recreational physical activity and breast cancer risk among women under age 45 years. Am J Epidemiol. In press.
(36) Sternfeld B, Williams CS, Queenberry CP, Satariano WA, Sidney S. Lifetime physical activity and incidence of breast cancer [abstract]. Med Sci Sports Exercise 1993;25(suppl 5):S147.
(37) Carpenter CL, Ross R, Paganini-Hill A, Bernstein L. Lifetime physical activity and breast cancer among postmenopausal women [abstract]. Am J Epidemiol 1996;143:S87.
(38) Marcus PM, Newman B, Millikan RC, Moorman PG, Baird DD, Stemfeld B, et al. The association of adolescent body mass index (BMI) and physical activity with breast cancer risk [abstract]. Am J Epidemiol 1997;145: S23.
(39) Giglia L. The relationship between physical activity and the risk of developing breast cancer. M.Sc. Thesis. 1992. University of Toronto. Cited in reference *(5)*.
(40) Cerhan J, Chiu J, Wallace R, Lemke J, Lynch C, Torner J, et al. Systolic blood pressure, physical activity, and risk of breast cancer in elderly women [abstract]. Am J Epidemiol 1996;143:S71.
(41) Sesso HD, Paffenbarger RS, Lee IM. Physical activity and breast cancer risk in the college alumni study [abstract]. Am J Epidemiol 1997; 145:S22.
(42) Frisch RE, Wyshak G, Albright NL, Albright TE, Schiff I, Jones KP, et al. Lower prevalence of breast cancer and cancers of the reproductive system among former college athletes compared to non-athletes. Br J Cancer 1985;52:885–91.
(43) Falkner KL, Trevisan M, McCann SE, Winkelstein W Jr. Influences on long-term recall of past physical activity: the Buffalo Health Study [abstract]. Am J Epidemiol 1997;145:S24.
(44) Vena JE, Graham S, Zielezny M, Brasure J, Swanson MK. Occupational exercise and risk of cancer. Am J Clin Nutr 1987;45(1 Suppl):318–27.
(45) Vihko VJ, Apter DL, Pukkala EI, Oinonen MT, Hakulinen TR, Vihko RK. Risk of breast cancer among female teachers of physical education and languages. Acta Oncol 1992;31:201–4.
(46) Zheng W, Shu XO, McLaughlin JK, Chow WH, Gao YT, Blot WJ. Occupational physical activity and the incidence of cancer of the breast, corpus uteri, and ovary in Shanghai. Cancer 1993;71:3620–4.
(47) Pukkala E, Poskiparta M, Apter D, Vihko V. Life-long physical activity and cancer risk among Finnish female teachers. Eur J Cancer Prev 1993; 2:369–76.
(48) Dosemeci M, Hayes RB, Vetter R, Hoover RN, Tucker M, Engin K, et al. Occupational physical activity, socioeconomic status, and risk of 15 cancer sites in Turkey. Cancer Causes Control 1993;4:313–21.
(49) Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I. Follow-up data: diabetes, cholesterol, pulse, and physical activity. Cancer Epidemiol Biomarkers Prev 1995;4:807–11.
(50) Coogan PF, Newcomb PA, Clapp RW, Trentham-Dietz A, Baron JA, Longnecker MP. Physical activity in usual occupation and risk of breast cancer (United States). Cancer Causes Control 1997;8:626–31.
(51) Garfinkel L, Stellman SD. Mortality by relative weight and exercise. Cancer 1988;62(8 Suppl):1844–50.
(52) Thune I, Lund E. Exercise and breast cancer [letter]. N Engl J Med 1997;337:709.
(53) Michels-Blanck H, Byers T, Mokdad AH, Will JC, Calle EE. Menstrual patterns and breast cancer mortality in a large U.S. cohort. Epidemiology 1996;7:543–6.
(54) Thompson HJ. Effect of exercise intensity and duration on the induction of mammary carcinogenesis. Cancer Res 1994;54(7 Suppl): 1960s–1963s.
(55) Cohen LA. Physical activity and cancer. Cancer Prev 1991;26:1–10.
(56) Key TA, Pike MC. The role of oestrogens and progestagens in the epidemiology and prevention of breast cancer. Eur J Cancer Clin Oncol 1988;24:29–43.
(57) Bernstein L, Ross RK. Endogenous hormones and breast cancer risk. Epidemiol Rev 1993;15:48–65.
(58) Pike MC, Spicer DV, Dahmoush L, Press MF. Estrogens, progestrogens, normal breast cell proliferation, and breast cancer risk. Epidemiol Rev 1993;15:17–35.
(59) Rosner B, Colditz GA, Willett WC. Reproductive risk factors in a prospective study of breast cancer: the Nurses' Health Study. Am J Epidemiol 1994;139:819–35.
(60) Colditz GA, Frazier AL. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. Cancer Epidemiol Biomarkers Prev 1995;4:567–71.
(61) Henderson BE, Ross RK, Judd HL, Krailo MD, Pike MC. Do regular ovulatory cycles increase breast cancer risk? Cancer 1985;56:1206–8.
(62) Bernstein L, Ross RK, Henderson BE. Prospects for the primary prevention of breast cancer. Am J Epidemiol 1992;135:142–52.
(63) Harlow SD, Matanoski GM. The association between weight, physical activity, and stress and variation in the length of the menstrual cycle. Am J Epidemiol 1991;133:38–49.
(64) Harlow SD, Ephross SA. Epidemiology of menstruation and its relevance to women's health. Epidemiol Rev 1995;17:265–86.
(65) Malina RM, Spirduso WW, Tate C, Baylor AM. Age at menarche and selected menstrual characteristics in athletes at different competitive levels and in different sports. Med Sci Sports 1978;10:218–22.
(66) Frisch RE, Wyshak G, Vincent L. Delayed menarche and amenorrhea in ballet dancers. N Engl J Med 1980;303:17–9.
(67) Frisch RE, Gotz-Welbergen AV, McArthur JW, Albright T, Witschi J, Bullen B, et al. Delayed menarche and amenorrhea of college athletes in relation to age at onset of training. JAMA 1981;246:1559–63.
(68) Moisan J, Meyer F, Gingras S. Leisure physical activity and age at menarche. Med Sci Sports Exerc 1991;23:1170–5.
(69) Merzenich H, Boeing H, Wahrendorf J. Dietary fat and sports activity as determinants for age at menarche. Am J Epidemiol 1993;138:217–24.
(70) Meyer F, Moisan J, Marcoux D, Bouchard C. Dietary and physical determinants of menarche. Epidemiology 1990;1:377–81.
(71) Sowers MR, La Pietra MT. Menopause: its epidemiology and potential association with chronic diseases. Epidemiol Rev 1995;17:287–302.

(72) Bromberger JT, Matthews KA, Kuller LW, Wing RR, Meilahn EN, Plantinga P. Prospective study of the determinants of age at menopause. Am J Epidemiol 1997;145:124–33.
(73) Otis CL. Exercise-associated amenorrhea. Clin Sports Med 1992;11: 351–62.
(74) Cumming DC, Wheeler GD, Harber VJ. Physical activity, nutrition, and reproduction. Ann N Y Acad Sci 1994;709:55–76.
(75) Cooper GS, Sandler DP, Whelan EA, Smith KR. Association of physical activity and behavioral characteristics with menstrual cycle patterns in women age 29–31 years. Epidemiology 1996;7:624–8.
(76) Loucks AB, Mortola JF, Girton L, Yen SS. Alterations in the hypothalamic–pituitary–ovarian and the hypothalamic–pituitary–adrenal axes in athletic women. J Clin Endocrinol Metab 1989;68:402–11.
(77) Broocks A, Pirke KM, Schweiger U, Tuschl RJ, Laessle RG, Strowitzki T, et al. Cyclic ovarian function in recreational athletes. J Appl Physiol 1990;68:2083–6.
(78) Apter D, Vihko R. Early menarche, a risk factor for breast cancer, indicates early onset of ovulatory cycles. J Clin Endocrinol Metab 1983;57: 82–6.
(79) Ballard-Barbash R, Swanson CA. Body weight: estimation of risk for breast and endometrial cancers. Am J Clin Nutr 1996;63(3 Suppl):437S-41S.
(80) Hunter DJ, Willett WC. Nutrition and breast cancer. Cancer Causes Control 1996;7:56–68.
(81) Enriori CL, Reforzo-Membrives J. Peripheral aromatization as a risk factor for breast and endometrial cancer in postmenopausal women: a review. Gynecol Oncol 1984;17:1–21.
(82) Zumoff B. Hormonal abnormalities in obesity. Acta Med Scand Suppl 1988;723:153–60.
(83) Slattery ML, McDonald A, Bild DE, Caan BJ, Hilner JE, Jacobs DR Jr, et al. Associations of body fat and its distribution with dietary intake, physical activity, alcohol, and smoking in blacks and whites. Am J Clin Nutr 1992;55:943–9.
(84) Siiteri PK. Adipose tissue as a source of hormones. Am J Clin Nutr 1987;45(1 Suppl):277–82.
(85) Hill JO, Drougas HJ, Peters JC. Physical activity, fitness, and moderate obesity. In: Bouchard C, Shepard RJ, Stephens T, editors. Physical activity, fitness, and health: international proceedings and consensus statement. Champagne (IL): Human Kinetics Publications, 1994:684–95.
(86) Kohrt WM, Obert KA, Holloszy JO. Exercise training improves fat distribution patterns in 60- to 70-year-old men and women. J Gerontol 1992; 47:M99–105.
(87) Cumming DC, Vickovic MM, Wall SR, Fluker MR. Defects in pulsatile LH release in normally menstruating runners. J Clin Endocrinol Metab 1985;60:810–2.
(88) Bonen A, Long WY, MacIntyre KP, Neil R, McGrail JC, Belcastro AN. Effects of exercise on the serum concentrations of FSH, LH, progesterone, and estradiol. Eur J Appl Physiol 1979;42:15–23.
(89) Bonen A, Belcastro AN, Ling WY, Simpson AA. Profiles of selected hormones during menstrual cycles of teenage athletes. J Appl Physiol 1981;50:545–51.
(90) Bullen BA, Skrinar GS, Beitins IZ, Carr DB, Reppert SM, Dotson CO, et al. Endurance training effects on plasma hormonal responsiveness and sex hormone excretion. J Appl Physiol 1984;56:1453–63.
(91) Baker ER, Mathur RS, Kirk RF, Williamson HO. Female runners and secondary amenorrhea: correlation with age, parity, mileage, and plasma hormonal and sex-hormone-binding globulin concentrations. Fertil Steril 1981;36:183–7.
(92) Loucks AB, Horvath SM. Exercise-induced stress responses of amenorrheic and eumenorrheic runners. J Clin Endocrinol Metab 1984;59: 1109–20.
(93) Boyden TW, Pamenter RW, Stanforth P, Rotkis T, Wilmore JH. Sex steroids and endurance running in women. Fertil Steril 1983;39:629–32.
(94) Fisher EC, Nelson ME, Frontera WR, Turksoy RN, Evans WJ. Bone mineral content and levels of gonadotropins and estrogens in amenorrheic running women. J Clin Endocrinol Metab 1986;62:1232–6.
(95) Prior JC, Cameron K, Yuen BH, Thomas J. Menstrual cycle changes with marathon training: anovulation and short luteal phase. Can J Appl Sport Sci 1982;7:173–7.
(96) Ellison PT, Lager C. Moderate recreational running is associated with lowered salivary progesterone profiles in women. Am J Obstet Gynecol 1986;154:1000–3.
(97) Cauley JA, Gutai JP, Kuller LH, LeDonne D, Powell JG. The epidemiology of serum sex hormones in postmenopausal women. Am J Epidemiol 1989;129:1120–31.
(98) Nelson ME, Meredith CN, Dawson-Hughes B, Evans WJ. Hormone and bone mineral status in endurance-trained and sedentary postmenopausal women. J Clin Endocrinol Metab 1988;66:927–33.
(99) Newcomb PA, Klein R, Klein BE, Haffner S, Mares-Perlman J, Cruickshanks KJ, et al. Association of dietary and life-style factors with sex hormones in postmenopausal women. Epidemiology 1995;6:318–21.
(100) Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, Banerjee S, Koenig KL, Shore RE, et al. A prospective study of endogenous estrogens and breast cancer in postmenopausal women. J Natl Cancer Inst 1995;87: 190–7.
(101) Dorgan JF, Longcope C, Stephenson HE Jr, Falk RT, Miller R, Franz C, et al. Relation of prediagnostic serum estrogen and androgen levels to breast cancer risk. Cancer Epidemiol Biomarkers Prev 1996;5:533–9.
(102) Shephard RJ, Shek PN. Cancer, immune function, and physical activity. Can J Appl Physiol 1995;20:1–25.
(103) Nieman DC. Exercise, upper respiratory tract infection, and the immune system. Med Sci Sports Exerc 1994;26:128–39.
(104) Pedersen BK, Ullum H. NK cell response to physical activity: possible mechanisms of action. Med Sci Sports Exerc 1994;26:140–6.
(105) Newsholme EA, Parry-Billings M. Effects of exercise on the immune system. In: Bouchard C, Shepard RJ, Stephens T, editors. Physical activity, fitness, and health. Champaign (IL): Human Kinetics Publishers, 1994:451–5.
(106) Kanter MM. Free radicals, exercise, and antioxidant supplementation. Int J Sport Nutr 1994;4:205–20.
(107) Ji LL. Exercise, oxidative stress, and antioxidants. Am J Sports Med 1996;24(6 Suppl):S20–4.

Note

Manuscript received August 1, 1997; revised October 31, 1997; accepted November 7, 1997.