FIRST LADY HILLARY RODHAM CLINTON
OUR NEW NATIONAL FOCUS ON ELIMINATING BREAST CANCER

October is Breast Cancer Awareness Month, and awareness could not come a moment too soon. Breast cancer has become an epidemic among American women. Who among us has not been tormented by breast cancer in our family, or among our friends or colleagues at work? This year alone, 46,000 women will die from breast cancer and 182,000 women will be newly diagnosed with the illness.

Breast cancer is the disease most feared by American women. It used to be spoken about only in whispers. But now, thanks to advances in public education, not only can we say the words, we also are conquering the fear. Until recently, a diagnosis of breast cancer was a death sentence. Today, thanks to significant strides in diagnosis and clinical care, medicine is adding years to the lives of women with the illness.

Two years ago this month, the President pledged a national commitment to stopping this killer of women. He established the National Action Plan on Breast Cancer -- being implemented today by the Public Health Service's Office on Women's Health -- a major public-private partnership involving all agencies of the federal government, breast cancer advocacy groups, health care professional organizations and private industry to develop innovative strategies in breast cancer research, service and education.

The Clinton Administration's commitment is reflected in a dramatic increase in funds dedicated to fight this disease. What in 1990 was a $90 million program of breast cancer research has grown to an investment of $600 million by the Administration today. These resources are dedicated to public education about breast cancer and the benefits of early diagnosis, as well as to the research that is bringing us new knowledge about the causes of breast cancer and, hopefully, one day, will bring a cure. This new national investment is beginning to yield dividends that are being measured in women's lives saved.

Our intensified efforts to understand the causes of breast cancer are paying off. This year, researchers discovered a gene, called BrCa1, thought to be related to 5% of all breast cancers and 25% of the breast cancers found in women under the age of 30. Another gene found in more than 2 million Americans -- ataxia telangiectasia mutated, or ATM for short -- has recently been found to place a woman at fivefold risk of developing breast cancer over her lifetime. With this knowledge, researchers are now working both to develop screening tests for these susceptibility genes and to develop ways to repair the genes so the disease does not occur.

But heredity explains only a small portion of the growing numbers of women with breast cancer. Over 90% of breast cancers are caused by environmental factors that alter or mutate the breast tissue to form cancerous tissue. The Administration is committed to fostering an understanding of these causes of breast cancer and eliminating them as well. Through new collaborations forged among our Federal agencies, we are learning about how environmental toxins in the atmosphere, the home or the workplace may act as triggers for the development of breast cancer.

We are learning how diet and exercise can help lower the risks of this disease. We all have read of the cancer preventive benefits of a low-fat diet that is rich in vegetables, fruit, and fiber; many of us are far more food conscious as a result. Recent promising breast cancer prevention news may help reverse America's growing tendency to skip exercise as part of our daily routine. A recent study found that the risk of developing breast cancer was reduced by half for young women, if they ran, played tennis, swam, or engaged in other modestly vigorous exercise for four or more hours a week. A sizable return on the time expended.

Until we can prevent breast cancer or find a cure for the disease, the focus for women today must be on its early detection, which provides the best chance for effective treatment. Mammography, a lifesaving technology, can significantly decrease death rates for women by finding the disease early, one to two years before it can be felt as a lump. In fact, for the first time in history, the overall death rate from breast cancer has declined. The decline is the direct result not only of improved treatment but also of increased use of regular mammograms.

Additionally, the Clinton Administration has taken major steps to improve the quality and safety of mammograms by implementing the Mammography Quality Standards Act requiring facilities to meet exacting standards of excellence. Effective July 1, 1995, all non-federal mammography facilities and mammography vans meeting these standards received an FDA "seal of approval." This certificate guarantees safe and accurate equipment, qualified technicians and radiologists to administer the test and read the results, and prompt notification of the results.

But mammography only works if it is used, and I have learned by speaking with many older women across the country, that one in three of Medicare age are not getting their mammograms. We've done something about that, too. In collaboration with the Health Care Financing Administration (the agency that administers the Medicare program) and the Public Health Service's Office on Women's Health, we launched a year-long national mammography Initiative last May to remind older women about Medicare's mammography screening benefit. You may have seen our "Mama-gram" campaign in honor of Mother's Day at grocery stores, florists,

and other establishments. You can help this effort by giving your mothers, sisters, aunts, cousins, or friends over 65 a free brochure "Get a Mammogram - A Picture That Can Save Your Life." Your local Social Security Office should have them on display.

But mammography is a 40-year old technology. In some cases it mistakes healthy tissue for cancer or misses a cancer altogether. So this Administration has committed itself to the development of a new generation of more accurate breast cancer detection tools, including the application of imaging technologies used for defense and intelligence purposes, that are more than a decade ahead of those in medical science today. This "Missiles to Mammograms" initiative has forged a unique collaboration among the Department of Health and Human Services, the Department of Defense and the Central Intelligence Agency to translate the science of detecting tank movements on a battlefield to the medicine of detecting cancerous tissue in a woman's breast.

Our dedication and commitment to bringing a halt to the breast cancer epidemic is being measured both in innovations in science and technology, and in new treatments and education programs for American women.

To find out where you can get a mammogram, how to help reduce your risk of breast cancer, and what treatment options are available if you or a loved one has breast cancer, call 1-800-4-CANCER, our National Cancer Institute's free information service. Working together, we can eliminate breast cancer as a significant threat to the lives of American women.

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Physical Exercise and Reduced Risk of Breast Cancer in Young Women

*Leslie Bernstein, Brian E. Henderson, Rosemarie Hanisch, Jane Sullivan-Halley, Ronald K. Ross**

Background: Epidemiologic evidence strongly suggests that cumulative exposure to ovarian hormones is a determinant of breast cancer risk. Because physical activity can modify menstrual cycle patterns and alter the production of ovarian hormones, it may reduce breast cancer risk; yet few epidemiologic studies have assessed this relationship. *Purpose:* The major objective of this study was to determine whether young women (aged 40 and younger) who regularly participated in physical exercise activities during their reproductive years had a reduced risk of breast cancer. *Methods:* Using a case–control design, we conducted personal interviews of a total of 545 women (aged 40 and younger at diagnosis) who had been newly diagnosed with in situ or invasive breast cancer between July 1, 1983, and January 1, 1989, and a total of 545 control subjects. Case patients and control subjects were individually matched on date of birth (within 36 months), race (white), parity (nulliparous versus parous), and neighborhood of residence. Lifetime histories of participation in physical exercise activities on a regular basis were obtained during the personal interview. *Results:* After adjustment for potential confounding factors, we found that the average number of hours spent in physical exercise activities per week from menarche to 1 year prior to the case patient's diagnosis was a significant predictor of reduced breast cancer risk (two-sided P for trend <.0001). The odds ratio (OR) of breast cancer among women who, on average, spent 3.8 or more hours per week participating in physical exercise activities was 0.42 (95% confidence limits [CLs] = 0.27, 0.64) relative to inactive women. The effect was stronger among women who had had a full-term pregnancy. Comparing most active (≥3.8 hours/wk of exercise) women to inactive women, the ORs were 0.28 (95% CL = 0.16, 0.50) for parous and 0.73 (95% CL = 0.38, 1.41) for nulliparous women. *Conclusions:* Most previously identified risk factors for breast cancer are reproductive and menstrual events that cannot be readily altered. The protective effect of exercise on breast cancer risk in the women whom we studied suggests that physical activity offers one modifiable lifestyle characteristic that may substantially reduce a woman's lifetime risk of breast cancer. *Implications:* Whether the protective effects of exercise on breast cancer risk are due to alterations in ovarian function and whether they extend into women's menopausal years need to be established. Our results suggest that implementation of regular physical exercise programs as a critical component of a healthy lifestyle should be a high priority for adolescent and adult women. [J Natl Cancer Inst 86:1403-1408, 1994]

Epidemiologic evidence strongly suggests that the cumulative number of ovulatory menstrual cycles and, hence, the cumulative exposure to ovarian hormones are determinants of breast cancer risk (*1,2*). The effects of early age at menarche and late age at menopause on breast cancer risk support this hypothesis (*3*). Early menarche is associated with more rapid onset of regular ovulatory menstrual cycles than late menarche (*4-6*). Time since menarche (generally referred to as gynecologic age) is also a predictor of frequency of ovulatory menstrual cycles during adolescence (*4-6*). Regardless of the age menarche begins, the rapidity with which regular cycling is established is related to breast cancer risk (*7*).

One implication of the accumulating evidence on the importance of ovulatory menstrual cycles is that any factor that modifies menstrual cycle patterns and reduces the frequency of ovulation may reduce a woman's lifetime risk of developing breast cancer. We have proposed that physical activity is such a factor (*6,8*). Strenuous exercise has profound effects on menstrual activity during adolescence (*9-13*); however, even participation in moderate levels of physical activity during adolescence can significantly reduce the frequency of ovulatory cycles (*6*). Several epidemiologic studies (*14-17*) have provided indirect evidence that physical activity may reduce the risk of breast cancer.

We recently completed a large case–control study of breast cancer among young women (aged 40 years and younger). A major objective of this study was to determine whether women who regularly participated in physical exercise activities during their reproductive years had a reduced risk of breast cancer.

Patients and Methods

All white female residents of Los Angeles County diagnosed with in situ or invasive breast cancer between July 1, 1983, and January 1, 1989, who were 40 years of age or younger at diagnosis, and who were born in the United States, Canada, or Europe, were eligible for participation in this study. Patients were identified by the University of Southern California Cancer Surveillance Program, the population-based cancer registry for Los Angeles County. Patients with a prior history of breast cancer were considered ineligible.

The Cancer Surveillance Program identified 969 eligible breast cancer patients, 949 (97.9%) of whom were alive when their physicians responded to our request for permission to contact their patients. Interviews were completed with 744 breast cancer patients (78.4% of living eligible case patients). Physicians refused permission to contact 54 women (5.6% of patients identified), and we were advised that an additional seven patients (<1%) could not be interviewed for reasons related to mental or physical health. Eligible patients were first contacted by letter and then telephoned to schedule an interview. A total of 111 patients (11.5%) refused to be interviewed. Twelve patients (1.2%) had moved outside Los Angeles County and could not be interviewed in person; 21 patients (2.2%) were lost to follow-up.

One neighborhood control subject was individually matched to each of the 744 interviewed

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See "Notes" section following "References."

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Physical Activity and Risk of Breast Cancer in the Framingham Heart Study

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Bernard E. Kreger,[3] Ralph B. D'Agostino,[4] Demetrius Albanes,[1] and Arthur Schatzkin[1]

The authors analyzed data from the Framingham Heart Study to evaluate the association between physical activity and breast cancer risk. Physical activity was ascertained by a physician-administered questionnaire from 2,321 women at the fourth biennial examination conducted in 1954–1956. Breast cancers were identified by self-report, surveillance of admissions to Framingham Union Hospital, and review of death records; all but one were histologically confirmed. During 28 years of follow-up, 117 breast cancer cases were diagnosed among the 2,307 women with data on physical activity and reproductive history (a potential confounder). Analysis was performed using Cox proportional hazards models with age as the underlying time variable. Models were adjusted for age at physical activity assessment, menopausal status, age at first pregnancy, parity, education, occupation, and alcohol ingestion. We observed a gradient of increasing risk of breast cancer with increasing physical activity (trend $p = 0.08$). The relative risk for women in the highest versus lowest activity quartile was 1.8 (95% confidence interval 0.8–3.0; $p = 0.13$). Although both moderate-to-heavy leisure and occupational activities were associated with an increased risk, the association was marginally significant only for leisure activity ($p = 0.06$). Our findings do not support a protective effect of physical activity during adulthood for breast cancer, but suggest an increased risk among more active women. *Am J Epidemiol* 1994;139:662–9.

breast neoplasms; exercise; prospective studies

Physical activity has been hypothesized to protect against breast cancer. Frisch et al. (1) first proposed a protective effect after observing a lower prevalence of breast cancer among former college athletes compared with nonathletes in a cohort of 5,398 living alumnae (relative risk = 0.5; 95 percent confidence interval (CI) 0.3–1.0). Paffenbarger et al. (2), however, failed to detect an association of breast cancer with participation in sports during the early college years. A nonsignificant inverse association between self-reported activity and postmenopausal breast cancer was observed for participants of the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (3). Relative risks for the most active versus least active women were 0.6 (95 percent CI 0.3–1.2) and 0.7 (95 percent CI 0.4–1.4), respectively, for recreational and nonrecreational activities. There was, however, a suggestion of an increased risk of premenopausal breast cancer among the more active women in this cohort. Occupational activity, surmised on the basis of job titles, [illegible] decreased risk of dying [illegible] in Washington State [illegible] whose usual lifetime [illegible] sified as nonsedentary, [illegible] ber of all deaths attrib[illegible] was significantly less [illegible] portionate mortality ra[illegible]

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Abbreviation: CI, confidence interval.

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case patients on birthdate (within 36 months), race (white), and parity (nulliparous versus parous). Control subjects were also restricted as to birthplace (United States, Canada, or Europe). To identify each neighborhood control subject, we established a predefined walk pattern for the neighborhood where the case patient lived at the time of her diagnosis. Housing units in the walk pattern were canvassed to determine whether a woman who matched the case patient on all characteristics lived in the household. If no one was home at the time of the visit, we left a request for information at the door, and we sought further information from neighbors so that we could contact the residents later. If we received no response to our written request for information, we telephoned the residence and sent additional letters until we were able to determine whether an eligible woman lived at the address in question.

Detailed records were maintained to determine the number of housing units contacted in order to identify and interview a matched control subject, the number of housing units in which no census was obtained, and the number of eligible residents who refused to participate. We contacted a median number of 32 housing units in order to interview a matched control subject for each case patient. To identify 15% of the control subjects, we had to canvass at least 130 housing units to recruit a single control subject. On the other hand, more than 25% of the participating matched control subjects were identified by canvassing fewer than 12 housing units. For 592 case patients, the first eligible control subject participated. For 124 case patients, one eligible person refused prior to the recruitment of a matched control subject. For the remaining 28 case patients, the number of refusals in the walk pattern ranged from two (for 18 case patients) to six (for two case patients). Complete censuses were obtained in the walk patterns for neighborhoods of 223 case patients. At some addresses, we were denied access to an apartment building; thus, the median number of unknowns in the walk patterns of the remaining case patients was four. The study was limited to white women because of the small representation of individual minority groups among young breast cancer patients in Los Angeles County and because of difficulties in ascertaining controls who fulfilled the strict matching and eligibility criteria (age, race, parity, birthplace) using the neighborhood control identification algorithm.

In-person interviews were conducted with all subjects by the same female nurse-interviewer (R. Hanisch). Signed, informed consent was obtained from each subject, and study procedures were approved by the University of Southern California Research Committee, in accord with assurances approved by the U.S. Department of Health and Human Services.

We obtained complete reproductive, contraceptive, and physical exercise histories for each participant. We recorded information on reproductive factors, oral contraceptive use, other hormone use, and physical exercise activities up to the date of the case patient's diagnosis for both case patients and control subjects and imposed time restrictions on these variables during the statistical analysis. A reference date, defined as the month and year that was 12 months prior to the date of the case patient's diagnosis, was assigned to each case-control pair. This date has been used as the cutoff date for accumulating the total months of participation in physical exercise activities and the total months of oral contraceptive use for each woman. A woman was considered to have a family history of breast cancer if she had a mother or sister who had been diagnosed with breast cancer.

At the beginning of the study, participants were asked to indicate physical exercise activities in which they participated at ages 10, 16, and 25. After interviews had been completed with 199 case–control pairs, we revised the questionnaire to assess lifetime history of regular participation (at least 2 hours/wk) in physical exercise. These activities included participation as a member of a sports team, including attendance at practice sessions; participation in individual sports, such as racquet sports, swimming, gymnastics, running/jogging, or walking for exercise; workouts at gyms; and participation in dance or exercise classes. Subjects provided the name of the activity, the ages at which they first and last participated in each continuous episode of the activity, and the number of hours per week of participation during each episode. Thus, when the level of participation in a particular activity changed, a separate episode was recorded. For each subject, we computed a measure of the average number of hours per week that the subject engaged in physical exercise between menarche and her reference date by summing up all of the hours of exercise and dividing by the total number of years between these two dates. We also assessed the hours of exercise in which each subject engaged during the first 10 years after menarche. This report is based on the 545 case–control pairs for whom we obtained complete histories on physical exercise.

The data were analyzed using univariate and multivariate conditional logistic regression methods for individually matched case–control studies (18). Relative risks were estimated by odds ratios (ORs) with 95% confidence limits (95% CLs). Tests for trend were calculated across categories. All significance levels reported (P values) are two-sided. For three case–control pairs, less than 10 years had elapsed between menarche and the reference date for at least one member of the pair; these pairs were considered to have missing information in the analysis of the average number of hours of physical exercise in the 10 years after menarche.

Results

At the time of their breast cancer diagnoses, the majority of case patients included in this study were between the ages of 36 and 40 years (≤30 years, 8.1%; 31-35 years, 28.6%; 36-40 years, 63.3%). Case patients and control subjects were closely matched on birthdate. Overall, the average age at diagnosis (±SE) of case patient was 36.0 years (±0.16). The average age of control subjects was 36.0 years (±0.17). Two hundred case–control pairs (36.7%) were nulliparous. The distributions of potential confounding factors that were considered in the multivariate logistic regression analyses are summarized for case patients and control subjects in Table 1.

The distributions of the average number of hours per week of participation in physical exercise between menarche and reference date and during the 10 years after menarche are shown in Table 2 for case patients and control subjects. A total of 194 case patients (35.6%) and 154 control subjects (28.3%) reported no activities during the time period under consideration. For both exercise factors, we created approximate quartiles based on the distribution of control subjects who reported any activity. After adjustment for age at menarche, age at first full-term pregnancy, number of full-term pregnancies, months of lactation, first-degree family history of breast cancer, Quetelet's index at reference date, and total months of oral contraceptive use, the risk of breast cancer decreased in a linear fashion with increasing number of hours per week in which a woman participated in physical exercise activities between menarche and her reference date (P = .00011).

Among women who averaged at least 3.8 hours of exercise activity per week during this time period, the odds of breast cancer were 0.42 (95% CL = 0.27, 0.64) relative to that of inactive women. When the data were restricted to exercise activities in which women participated during the 10 years after menarche, the decline in breast cancer risk with increasing activity level was statistically significant (P = .027); the odds of breast cancer for women who averaged at least 5.6 hours of physical exercise per week during these 10 years relative to inactive women was 0.70 (95% CL = 0.47, 1.06). The addition of months of activity after this 10-year time period to the multivariate logistic regression model significantly improved the fit of the model (P = .0001).

At the reference date (1 year prior to the case patient's diagnosis), 102 control subjects (18.7%) and 91 case patients (16.7%) were unemployed. Although this employment status does not represent the lifetime employment history of these women, we used it to assess whether being at home offered more time for regular exercise and thus would explain the protective effects of physical exercise activity on breast cancer risk. Adjusting for employment status had no effect on the

Table 1. Distribution of potential confounding factors in 545 breast cancer case patients and matched control subjects

Factor	No. of cases (%)	No. of controls (%)
Age at menarche, y		
≤11	158 (28.9)	119 (21.8)
12	156 (28.6)	166 (30.4)
13	150 (27.5)	151 (27.7)
≥14	81 (14.9)	109 (20.0)
Age at first term pregnancy*, y		
≤19	74 (21.4)	90 (26.1)
20-24	114 (33.0)	132 (38.3)
25-29	103 (29.9)	75 (21.7)
30-34	41 (11.9)	36 (10.4)
≥35	13 (3.8)	12 (3.5)
No. of full-term pregnancies*		
1	101 (29.3)	90 (26.1)
2	162 (47.0)	151 (43.8)
3	53 (15.4)	75 (21.7)
≥4	29 (8.4)	29 (8.4)
Months of lactation*		
None	141 (40.9)	139 (40.3)
1-6	97 (28.1)	77 (22.3)
7-15	67 (19.4)	68 (19.7)
≥16	40 (11.6)	61 (17.7)
First-degree family history of breast cancer†		
No	459 (84.2)	505 (92.7)
Yes	79 (14.5)	33 (6.1)
Adopted	7 (1.3)	7 (1.3)
Quetelet's index‡		
≤20.2	120 (22.0)	137 (25.1)
20.3-22.0	155 (28.4)	137 (25.1)
22.1-24.9	138 (25.3)	137 (25.1)
≥25.0	132 (24.2)	134 (24.6)
Oral contraceptive use, mo		
None	94 (17.2)	82 (15.0)
1-48	240 (44.0)	241 (44.2)
49-96	112 (20.6)	139 (25.5)
97-144	60 (11.0)	59 (10.8)
≥145	39 (7.2)	24 (4.4)

*Parous pairs only
†Defined as having a mother or sister who had been diagnosed with breast cancer.
‡At reference date (12 months before the case patient's diagnosis) defined as weight (kg) divided by the square of height (m).

results presented in Table 2. Including separate physical activity categories for employed and unemployed women in the multivariate logistic regression model did not significantly improve its fit ($P = .53$), and the linear trends of declining breast cancer risk across categories of exercise activity were nearly identical (test for homogeneity of trends, $P = .48$).

We assessed the consistency of the inverse association of breast cancer risk and participation in physical exercise between menarche and the reference date in nulliparous and parous women by simultaneously fitting separate physical exercise terms for each group in the multivariate logistic model (Table 3). We compared this model to the relevant categorical and linear trend models presented in Table 2. Including separate physical activity categories for nulliparous and parous women in the multivariate logistic regression model did not significantly improve its fit ($P = .14$); however, there was a significant difference in the linear trends across categories (test for homogeneity of trends, $P = .029$). Comparing most active (≥3.8 hours of activity/wk) women to inactive women, we found that the relative odds of breast cancer were 0.28 (95% CL = 0.16, 0.50) among parous women and 0.73 (95% CL = 0.38, 1.41) among nulliparous women.

Within the group of nulliparous women, breast cancer risk was lower among those who had been married (multivariate OR = 0.73; 95% CL = 0.41, 1.29). Assuming that never-married women were less likely to be nulliparous because of an underlying ovarian problem than ever-married women, we assessed the effect of physical exercise on the breast cancer risk of women who had never married. Among never-married nulliparous women (71 case patients and 58 control subjects), participants in exercise activity had lower breast cancer risk (0.1-1.6 hours/wk, multivariate OR = 0.57; >1.7 hours/wk, multivariate OR = 0.48), although the results were not statistically significant (trend $P = 0.15$).

We found no evidence of modification of the effect of physical exercise on breast cancer risk by age at menarche (<13 years of age versus ≥13 years of age), months of oral contraceptive use (<36 months versus ≥ 36 months), or Quetelet's index at reference date (<23 years of age versus ≥23 years of age) or at age 18 (<21 years of age versus ≥21 years of age) (analyses not shown). For each of these factors, the trends in risk of breast cancer associated with increasing level of participation in physical exercise were statistically comparable and nearly identical to those shown in Table 2. Among parous women, there was no evidence of effect modification by age at first full-term pregnancy (<25 years versus ≥25 years), number of full-term pregnancies (one pregnancy versus two versus three or more pregnancies), or months of lactation (<6 months versus ≥6 months).

To further assess the possible impact of childbearing/child rearing on the protective effect of exercise in parous women, we created three additional variables: 1) months between first and last full-term pregnancy, 2) average number of months between full-term pregnancies, and 3) months since last full-term pregnancy. However, none of these factors was independently related to breast cancer risk. Furthermore, adjustment for these factors (in quartiles based on the distribution among control subjects) did not alter the results presented in Table 2.

We repeated all of the analyses, restricting subjects to those case–control pairs where the case patient had been diagnosed with invasive breast cancer (492/545 pairs). None of the results differed from those presented here. For example, in this subset of subjects, the risk of breast cancer declined significantly with increasing amounts of lifetime

Table 2. Univariate and multivariate ORs (95% CLs) for breast cancer associated with participation in physical exercise activities after menarche among women aged 40 years or younger

Hours of activity per week	No. of cases/No. of controls	Univariate OR (95% CL)	Multivariate OR (95% CL)*
Overall†			
None	194/154	1.0	1.0
0.1-0.7	103/90	0.92 (0.65, 1.32)	0.95 (0.64, 1.41)
0.8-1.6	84/102	0.66 (0.46, 0.95)	0.65 (0.45, 0.96)
1.7-3.7	103/100	0.82 (0.58, 1.17)	0.80 (0.54, 1.17)
>3.8	61/99	0.50 (0.34, 0.73)	0.42 (0.27, 0.64)
Test for linear trend across categories		P = .0007	P = .0001
Within the 10 years after menarche			
None	279/252	1.0	1.0
0.1-1.2	74/74	0.92 (0.64, 1.32)	0.93 (0.63, 1.38)
1.3-2.9	62/68	0.83 (0.57, 1.20)	0.78 (0.52, 1.19)
3.0-5.5	61/71	0.77 (0.52, 1.13)	0.69 (0.45, 1.05)
≥5.6	65/76	0.76 (0.53, 1.11)	0.70 (0.47, 1.06)
Test for linear trend across categories		P = .073	P = .027

*Adjusted for categories of age at menarche, age at first full-term pregnancy, number of full-term pregnancies, months of lactation, first-degree family history of breast cancer, Quetelet's index at reference date (12 months before the case patient's diagnosis), and total months of oral contraceptive use up to the reference date, as shown in Table 1.

†Average number of hours of participation per week between menarche and reference date.

physical exercise activity (P for trend = .0002). Among women who averaged at least 3.8 hours of activity per week during their reproductive lifetime, the multivariate relative odds of breast cancer were 0.40 (95% CL = 0.26, 0.62).

Discussion

Physical activity has demonstrable effects on the production of estrogen and other sex hormones. The acute hormonal response to exercise among untrained women includes increases in estradiol and progesterone levels, particularly in the luteal phase of the menstrual cycle, and an increase in the levels of follicle-stimulating hormone during the follicular phase (*19,20*). Over the long term, however, exercise training reduces the length of the luteal phase (*21,22*), lowers follicle-stimulating hormone levels (*19,21*) and average luteal phase progesterone levels (22), and often causes secondary amenorrhea, particularly during adolescence (*9-13*).

It has been reported that premenarcheal girls who engage in strenuous physical exercise regimens, such as regular ballet dancing, running, or swimming, may experience delay in the onset of menses (*11,23,24*). A prospective study (25) conducted in the Federal Republic of Germany demonstrated a statistically significant delayed menarche among girls who were more active in school and leisure-time sports. We (6) have previously shown that, in addition to age at menarche and gynecologic age, participation in moderate physical activity (at least 600 kcal of energy expenditure per week) significantly increases the likelihood that regularly menstruating adolescent girls will experience anovulatory menstrual cycles.

In this case–control study, we found a striking protective effect on breast cancer risk of continued participation in physical exercise activities during a woman's reproductive years, particularly among women of proven fertility. The effect among parous women is consistent with our hypothesis that habitual exercise should reduce the risk of breast cancer by

Table 3. Multivariate OR* (95% CL) for breast cancer associated with participation in physical exercise activities after menarche among nulliparous and parous women

Hours of activity per week†	Nulliparous women: No. of cases/No. of controls	Nulliparous women: OR (95% CL)	Parous women: No. of cases/No. of controls	Parous women: OR (95% CL)
None	59/53	1.0	135/101	1.0
0.1-0.7	36/35	0.81 (0.42, 1.57)	67/55	1.06 (0.65, 1.74)
0.8-1.6	27/38	0.65 (0.35, 1.21)	57/64	0.65 (0.40, 1.06)
1.7-3.7	46/41	0.94 (0.53, 1.67)	57/59	0.70 (0.42, 1.18)
≥3.8	32/33	0.73 (0.38, 1.41)	29/66	0.28 (0.16, 0.50)
Likelihood ratio test‡		P = .14		
Test for linear trend across categories		P = .43		P<.0001
Test for homogeneity of trends		P = .029		

*ORs are estimated simultaneously for parous and nulliparous women and are adjusted for categories of age at menarche, age at first full-term pregnancy, number of full-term pregnancies, months of lactation, first-degree family history of breast cancer, Quetelet's index at reference date (12 months before the case patient's diagnosis), and total months of oral contraceptive use up to the reference date, as shown in Table 1.

†Average number of hours of participation per week between menarche and reference date.

‡To assess whether fit of multivariate logistic regression model is improved by fitting separate activity categories for nulliparous and parous women (compared with overall model in Table 1).

altering menstrual function either by reducing the frequency of ovulatory menstrual cycles or by reducing the length of the luteal phase, thereby reducing the cumulative exposure to progesterone and estradiol. The protective effect of physical exercise did not appear to be mediated by an effect on body mass as, consistent with other studies of premenopausal breast cancer, there was no increased risk of breast cancer with increased Quetelet's index or other obesity indices. The effects of exercise were not modified appreciably by measures of childbearing or child rearing, such as age at first full-term pregnancy, number of full-term pregnancies, months of lactation, average spacing of births, time between first and last birth, or time since last birth. Our data suggest that women who maintain an activity level of 1-3 hours/wk could reduce their risk of premenopausal breast cancer by about 30% relative to inactive women and that those who maintain an activity level of at least 4 hours per week could reduce their risk by more than 50%.

Our inability to demonstrate a dose–response effect among nulliparous women may be due to the inclusion in this group of a subset of women who have an underlying ovarian problem. Using marital status as a surrogate to differentiate between two groups of nulliparous women with different likelihoods of having an ovarian problem, we observed that physical exercise appears to protect against breast cancer among never-married, nulliparous women, the group that is less likely to include women with such problems. Among women with anovulatory menstrual cycles or impaired luteal function, we might not expect an effect of physical activity on breast cancer risk, as this is the likely mechanism for the observed protection.

The protective effect of exercise on breast cancer risk in the women whom we studied was more pronounced when we considered the woman's complete exercise history than when we restricted our analyses to the activities during the 10 years after menarche. This finding emphasizes the importance of establishing lifelong patterns of physical activity.

The few epidemiologic studies that have assessed the relationship between physical activity and breast cancer risk have primarily used indirect measures of activity levels or have incompletely assessed breast cancer occurrence. Frisch et al. (*14*) compared the prevalence of breast cancer among female college athletes and nonathletes in a follow-up study of college alumni from the classes of 1925-1981; they relied on self-reports of cancer and excluded women who had died. Nonathletes had an 86% greater subsequent risk of breast cancer than did athletes. Among ever-pregnant women, the effect was more pronounced with nonathletes having a twofold greater risk than athletes, consistent with our observation among parous women.

Vena et al. (*15*) conducted a study of mortality by occupation among female residents in Washington State between 1974 and 1979. They evaluated differences in physical activity associated with the "usual" occupation recorded on death certificates. The proportionate mortality ratio (PMR) for breast cancer was significantly elevated (PMR = 115) for women in the lowest category of occupational activity and significantly decreased for those in the three highest activity levels (PMR = 85).

In the NHANES I (National Health and Nutrition Examination Survey, National Center for Health Statistics) Epidemiologic Follow-up Study (*16*), in which participants rated both their usual nonrecreational activity and their usual recreational exercise on a 3-point ordinal scale, the risk of postmenopausal breast cancer was nonsignificantly elevated among "inactive" women. A retrospective follow-up study (*17*) of physical education and language teachers in Finland showed that language teachers had higher breast cancer risk than physical education teachers prior to menopause. Among these women, the differences in physical activity levels declined with increasing age. The postmenopausal breast cancer risk of physical education teachers was only slightly lower than that of the language teachers.

Data on the health benefits of physical activity continue to accumulate as physical activity appears to have a protective effect against a number of chronic conditions, including coronary heart disease, diabetes mellitus, osteoporosis, and colon cancer risk (*26-28*), and possibly, as suggested by recent evidence (*29*), against endometrial cancer risk (*29*). Our data strongly suggest that continued participation in a physical exercise regimen can markedly reduce the risk of breast cancer in premenopausal women and emphasize the importance of beginning an exercise regimen early in life and maintaining it during adulthood.

Despite these important benefits of physical activity, surveys of high school students (*30,31*) and adults (*32*) in the United States and adolescents in Britain (*33*) suggest that few young people, particularly few young women, are physically active. In the United States, for example, the 1990 Youth Risk Behavior Survey indicated that fewer than 40% of young women in their junior and senior years of high school were enrolled in physical education classes (*30*); and only 20% of such students participated in vigorous physical activity three or more times a week (*31*). Our results strongly support the need for educational policies that require participation in physical education classes and that encourage lifelong participation in exercise programs.

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Notes

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