Association of Physical Activity with Hormone Receptor Status: The Shanghai Breast Cancer Study

Swann Arp Adams,[1,3] Charles E. Matthews,[5] James R. Hebert,[1,3,6] Charity G. Moore,[7] Joan E. Cunningham,[2] Xiou-Oi Shu,[5] Jeanette Fulton,[4] Yutang Gao,[8] and Wei Zheng[5]

[1]The Cancer Prevention and Control Program and Department of Epidemiology and Biostatistics and [2]Department of Obstetrics and Gynecology, School of Medicine, University of South Carolina; [3]South Carolina Cancer Center; [4]South Carolina Comprehensive Breast Center, Columbia, South Carolina; [5]Division of General Internal Medicine and Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, Tennessee; [6]Cancer Prevention and Control Program, Hollings Cancer Center, Charleston, South Carolina; [7]Departments of Medicine and Biostatistics, University of North Carolina, Chapel Hill, North Carolina; and [8]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, People's Republic of China

Abstract

Evidence exists that breast tumors differing by estrogen receptor (ER) and progesterone receptor (PR) status may be phenotypically distinct diseases resulting from dissimilar etiologic processes. Few studies have attempted to examine the association of physical activity with breast cancer subtype. Such research may prove instructive into the biological mechanisms of activity. Consequently, this investigation was designed to assess the relationship between physical activity and hormone receptor-defined breast cancers in a population of Asian women in which the distribution of receptor types differed from traditional Western populations. Participants, ages 25 to 64 years, were recruited into this population-based, case-control study of breast cancer conducted in Shanghai, China from August 1996 to March 1998. Histologically confirmed breast cancer cases with available receptor status information (*n* = 1001) and age frequency-matched controls (*n* = 1,556) completed in-person interviews. Polytomous logistic regression was used to model the association between measures of activity with each breast cancer subtype (ER+/PR+, ER−/PR−, ER+/PR−, and ER−/PR+) using the control population as the reference group. Exercise in both adolescence and the last 10 years was associated with a decreased risk of both receptor-positive (ER+/PR+) and receptor-negative (ER−/PR−) breast cancers in both premenopausal and postmenopausal women (odds ratios, 0.44 and 0.51 and 0.43 and 0.21, respectively). Sweating during exercise within the last 10 years was also associated with decreased risk for receptor-positive and receptor-negative breast cancers among postmenopausal women (odds ratios, 0.58 and 0.28, respectively). These findings suggest that physical activity may reduce breast cancer risk through both hormonal and nonhormonal pathways. (Cancer Epidemiol Biomarkers Prev 2006;15(6):1170–8)

Introduction

On a global scale, breast cancer is the most frequently diagnosed cancer among women, accounting for ~23% of all cancers (1). Incidence rates of breast cancer among Chinese women have traditionally been roughly one third the rate of women in Western populations, such as the United States (18.7/100,000 versus 99.4/100,000; ref. 1). Recent evidence, however, has revealed that breast cancer rates seem to be climbing in China at ~3% to 4% yearly, especially within urbanized regions, such as Shanghai (1).

Many biological markers have been shown to have a significant effect on breast cancer relapse and, ultimately, death (2). Among these are estrogen receptor (ER) and progesterone receptor (PR) status of the tumor at diagnosis (3-6). Previous research shows that hormone-related factors, such as age at menarche, parity, and age at menopause, tend to be associated with receptor-positive (ER+/PR+) breast cancer, whereas family history of breast cancer and cigarette smoking have been associated with receptor-negative (ER−/PR−) breast cancer (7-16). These findings suggest that breast cancer does not represent a single phenotype (i.e., that it is *not* a homogeneous disease) but rather a heterogeneous set of diseases with perhaps different genetic and environmental determinants.

The majority of published studies (17-20) have indicated that high levels of physical activity confer a protective effect on breast cancer with proposed biological mechanisms ranging from hormone modulation to up-regulated immune functioning (21). Interestingly, the association between physical activity and breast cancer has not been seen consistently across all studies (22-33), with some studies showing either a null or a positive (i.e., detrimental) effect of physical activity on breast cancer risk.

One area that has not been studied extensively that could explain some of these conflicting reports is the association of physical activity with hormone receptor-defined breast cancer. Thus, it is possible that physical activity may be differentially associated with the various types of receptor-defined breast cancers. Furthermore, characterizing these associations may provide useful clues that will extend our understanding of the mechanism of action of physical activity on breast cancer. The Shanghai Breast Cancer Study (SBCS) offered a unique opportunity to examine this hypothesis among a population of women with a different distribution of hormone receptor subtype than more traditional Western populations. Previous research in the SBCS concluded that lifetime physical activity was associated with a significant reduction in overall breast cancer risk (30). Within the United States, typically only ~10% of all breast tumors are receptor negative; however, 26% of the breast tumors in the SBCS were receptor negative. The greater frequency lends greater power to stratified analyses of breast cancer receptor type. Consequently, the purpose of this

Received 12/29/05; revised 3/21/06; accepted 4/24/06.

Grant support: USPHS, National Cancer Institute grant R01CA64277; American College of Sports Medicine Foundation, Paffenbarger Fellowship Fund for Epidemiological Research on Physical Activity (S.A. Adams).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Swann Arp Adams, South Carolina Cancer Prevention and Control Program, University of South Carolina, Room 241, 2221 Devine Street, Columbia, SC 29208. Phone: 803-734-4484; Fax: 803-734-5259. E-mail: swann.adams@sc.edu

doi:10.1158/1055-9965.EPI-05-0993

investigation was to examine the association between physical activity and breast cancer by receptor status among women participating in the SBCS.

Materials and Methods

Subjects in this study were recruited from August 1996 to March 1998 as part of the SBCS, a population-based, case-control study of breast cancer conducted in urban Shanghai, China (30, 34). The SBCS protocol was approved by the relevant institutional review boards and informed consent was obtained from all study participants.

Subjects. All participants were permanent residents of Shanghai and were ages 25 to 64 years during the study period. Histologically confirmed breast cancer cases were recruited via a rapid case-ascertainment system of the Shanghai Cancer Registry. A total of 1,602 individuals with breast cancer were determined to be eligible for the study (alive at the time of interview and having no prior history of cancer). Of these, 1,459 (92% of those eligible) women completed the in-person interview. Refusal, death, or inability to locate the subject were the primary reasons for nonparticipation.

Female controls were recruited randomly from the general population of Shanghai through a resident registry system. Controls were frequency matched to cases on age by 5-year interval. Data were obtained on 1,556 women (90.3% of the 1,724 eligible), with refusal (9.6%) as the primary reason for nonparticipation.

Study Procedures

Data Collection. Trained interviewers administered a structured questionnaire designed to collect information on basic demographics: menstrual, reproductive, medical, family, and weight history; hormone usage; diet; physical activity behaviors; and alcohol use. For the case subjects, the average time between diagnosis and interview was 5 months. At the time of interview, current body measurements, including weight and height, were obtained on all participants using standard protocols. Participants were instructed to wear light clothing. Shoes were removed for the height measurements but not for weight measurements. Height and weight were measured twice. A third measurement was taken if the difference between the first two measures was significant (>1 kg for weight and >1 cm for height). The average of the two measures was used for this analysis.

Physical Activity. Information on occupational, household, transportation, and leisure-time physical activity was ascertained on all participants. Occupational activity was based on standardized job classifications (30) for all positions held by an individual woman for at least 3 years. Due to the stability of occupations within China, this period is adequate to capture the majority of occupations held by the individual (30). The average number of jobs held by women in this population was 2, whereas the average duration of a single job was 14.3 years. Subjects also reported the number of years spent at each job as well as estimates of total time spent standing or walking per day. Time spent sitting and average energy expenditure were classified into three levels (high, medium, or low) using job codes from the >200 occupations reported (30). For example, occupations, such as clerk or accountant, would have a ''high'' sitting and a ''low'' energy expenditure classification. This classification was then multiplied by the number of years spent on the job; the scores for each job were then summed to create overall scores for time spent sitting, average energy expenditure, and physical activity level (self-evaluation). Total occupational standing or walking time was calculated by multiplying the reported time spent standing or walking for each job by the duration of the job and then summing the values across all jobs.

Participants reported on their household, transportation, and leisure-time physical activity in adolescence (ages 13-19 years) and adulthood (last 10 years before the interview date). Transportation (biking and walking) and household physical activity were reported as the total time (per day or week) spent in each activity domain [i.e., ''how many hours per day did you spend on housework?'' and ''how many minutes did you walk each day (including walking to work, shopping, sending, or picking up children)?'']. For leisure-time activity estimates, subjects indicated the five most common sports activities in which they participated in the period of interest. Duration (per week) estimates were obtained for all reported activities. From these variables, summary estimates [metabolic equivalent (MET)-hours/d/y] for physical activity were created using the standard MET classifications (35, 36). Based on responses to the sports questions, a single lifetime activity variable was created with four groups: activity in adolescence and adulthood, no activity in adolescence or adulthood, activity in adolescence but not adulthood, and no activity in adolescence but reported in adulthood. Participants also were asked to rate the amount of time spent in leisure activity in comparison with other persons using a Likert-type response (i.e., ''more than average,'' ''a little more than average,'' ''about average,'' ''a little less than average,'' and ''less than average''). For those reporting leisure-time activity, respondents were asked to evaluate the frequency of sweating during exercise (i.e., ''sweated every time,'' ''sweated most of the time,'' or ''normally did not sweat'').

ER and PR Status. Data on ER and PR status based on medical record review were available for 1,001 (69%) of the 1,459 breast cancer cases. Only qualitative values (positive or negative) were collected. ER and PR status were designated as either positive or negative resulting in the following joint categories: ER+/PR+ (receptor-positive), ER−/PR+ (mixed), ER+/PR− (mixed), and ER−/PR− (receptor-negative).

Statistical Methods. All analyses were conducted using SAS (version 9.1) and an α, type I error, level of 0.05 (two-tailed) for statistical tests. The distributions or frequency of all variables were reviewed and descriptive statistics were computed. The distributions for leisure-time physical activity in adolescence and adulthood were highly skewed approximating a χ^2 distribution. To attenuate the leverage effect of the few observations in the higher range and to simplify the interpretation of these findings, the variables were categorized. All nonexercisers were classified as 0. The exercising group was categorized as greater than or equal to or less than the median value (1.92 MET-hours/d/y for adolescence and 0.875 MET-hours/d/y for adulthood) for the control population. Other physical activity variables included a comparison of time spent in activity relative to others, sweating during exercise, lifetime activity, occupational sitting, occupational walking, occupational activity self-rating, average occupational energy expenditure, household activity, and walking for transportation. Polytomous logistic regression was used to model the relationship between the physical activity summary variable and breast cancer tumor subtype (37), with the control group as the reference population. Each physical activity variable was assessed in a separate model. Due to the potential biological differences, effect modification of physical activity by menopausal status was assessed by including an interaction term in initial models. Because many of the *P*s of the Wald statistic for these interaction terms showed marginal significance, all models were stratified by menopausal status and adjusted for those variables that previous analysis using polytomous logistic modeling found to be significantly associated with breast cancer subtype. Models among premenopausal women were adjusted for current age, age at first menarche, age at first birth, parity, and breast-feeding, whereas postmenopausal models were adjusted for these previous variables and for age at menopause. For women who were nulliparous, the value for the variable ''months of breast-feeding'' was set as 0 and the value for the variable ''age at first live birth'' was designated as either current age (for premenopausal women) or age at menopause (for postmenopausal women). Body mass index [weight (kg) / height (m^2)] was included in all initial models; yet, all point estimates remained unchanged (<10% difference in b estimates) with no evidence for confounding or effect modification. Thus, final models excluded this variable. Results are presented as odds ratios (OR).

Results

Of the breast cancer cases, 529 (53%) of 1,001 with known ER/PR status were receptor-positive, 259 (26%) were receptor-negative, 108 (11%) were ER+/PR−, and 105 (10%) were ER−/PR+. Population characteristics are described in Tables 1 and 2. Most variables showed similar distributions among the five groups. As might be expected, controls tended to have a lower frequency of a family history of breast cancer and were less likely to have a personal history of fibroadenoma among premenopausal women. Among postmenopausal women, many of the body habitus measures tended to be lowest for the control group. For most of the physical activity measures, the case groups reported less physical activity than did controls among premenopausal women. This pattern was less consistent among premenopausal women, with case groups reporting greater levels of activity for some of the measures.

Consistent with previous reports from this study (30), physical activity showed a protective effect on overall breast cancer risk (results were not stratified by ER and PR type). Activity in both adolescence and within the last 10 years resulted in a 48% decrease (Ps < 0.01) in risk for premenopausal women and a 63% decrease (Ps < 0.0001) for postmenopausal women. Other activity variables for which a statistically significant protective effect on overall breast cancer risk was observed included sweating during exercise within the last 10 years, leisure activity measured by MET-hours/d/y, and self-comparison (data not shown).

The multivariable-adjusted estimates of the association of leisure-time activity with each breast cancer hormone receptor type are presented for premenopausal and postmenopausal women in Tables 3 and 4, respectively. The majority of point estimates showed a trend for a protective effect for physical

Table 1. Comparison of subjects by case-control status, SBCS, 1996-1998, % (*n*) or mean ± SD (range)

Variable	ER+/PR+	ER−/PR−	ER+/PR−	ER−/PR+	Control
Premenopausal					
Education (grade)					
≤8th	3 (9)	5 (10)	4 (3)	4 (3)	3 (29)
>8th	97 (337)	95 (175)	96 (69)	96 (69)	97 (961)
History of breast cancer in first-degree relative					
Yes	3 (10)	4 (7)	3 (2)	4 (3)	2 (19)
No	97 (336)	96 (178)	97 (70)	96 (69)	98 (971)
Ever pregnant					
Yes	97 (337)	97 (179)	92 (66)	96 (69)	97 (962)
No	3 (9)	3 (6)	8 (6)	4 (3)	3 (28)
No. pregnancies					
0	3 (9)	3 (6)	8 (6)	4 (3)	3 (28)
1-2	62 (213)	67 (123)	59 (42)	58 (42)	61 (607)
≥3	35 (124)	30 (56)	33 (24)	38 (27)	36 (355)
History of fibroadenoma					
Yes	10 (34)	6 (11)	6 (4)	11 (8)	5 (54)
No	90 (312)	94 (174)	94 (68)	89 (64)	95 (936)
Age (y)	44 ± 5.0 (28-57)	44 ± 5.3 (28-59)	43 ± 5.5 (30-55)	43 ± 4.2 (32-51)	42 ± 5.3 (25-58)
Age of first pregnancy (y)*	28 ± 4.1 (20-52)	28 ± 4.2 (19-50)	29 ± 5.9 (22-49)	29 ± 4.8 (23-47)	28 ± 3.9 (17-50)
Age at menarche (y)	14 ± 1.5 (10-19)	14 ± 1.5 (11-18)	14 ± 1.4 (11-18)	14 ± 1.6 (12-19)	15 ± 1.6 (10-21)
Waist-to-hip ratio (cm)	0.80 ± 0.06 (0.66-1.19)	0.80 ± 0.05 (0.69-0.95)	0.81 ± 0.06 (0.65-0.92)	0.79 ± 0.05 (0.68-0.93)	0.79 ± 0.06 (0.66-1.21)
Weight (kg)	59.0 ± 7.9 (38-86)	57.9 ± 8.2 (41-88)	59.2 ± 9.6 (41-95)	59.3 ± 9.3 (39-82)	57.7 ± 8.4 (34-100)
Body mass index (kg/m^2)	23.1 ± 2.9 (15.9-33.2)	22.8 ± 2.9 (17.0-35.2)	23.2 ± 3.5 (16.0-36.1)	23.0 ± 3.4 (14.3-31.5)	22.7 ± 3.2 (14.9-42.2)
Postmenopausal					
Education (grade)					
≤8th	24 (44)	34 (25)	28 (10)	18 (6)	33 (187)
>8th	76 (139)	66 (49)	72 (26)	82 (27)	67 (379)
History of breast cancer in first-degree relative					
Yes	3 (6)	7 (5)	3 (1)	3 (1)	3 (19)
No	97 (177)	93 (69)	97 (35)	97 (32)	97 (547)
Ever pregnant					
Yes	97 (178)	96 (71)	100 (36)	97 (32)	97 (549)
No	3 (5)	4 (3)	0 (0)	3 (1)	3 (17)
No. pregnancies					
0	3 (5)	4 (3)	0 (0)	3 (1)	3 (17)
1-2	31 (57)	22 (16)	28 (10)	27 (9)	27 (154)
≥3	66 (121)	74 (55)	72 (26)	70 (23)	70 (395)
History of fibroadenoma					
Yes	9 (16)	11 (8)	0 (0)	9 (3)	4 (24)
No	91 (167)	89 (65)	100 (36)	90 (30)	96 (542)
Age (y)	57 ± 5.1 (42-64)	57 ± 5.7 (34-64)	56 ± 5.4 (40-64)	56 ± 5.6 (43-64)	56 ± 5.5 (32-64)
Age of first pregnancy (y)*	26 ± 5.7 (17-52)	25 ± 6.7 (17-51)	25 ± 4.0 (18-33)	26 ± 5.4 (17-39)	25 ± 5.6 (16-55)
Age at menarche (y)	15 ± 1.8 (11-20)	15 ± 1.7 (11-18)	15 ± 1.6 (11-18)	14 ± 2.0 (11-19)	15 ± 1.9 (11-22)
Age at menopause (y)	48 ± 4.2 (28-58)	48 ± 5.1 (28-67)	50 ± 4.3 (34-58)	48 ± 4.8 (38-57)	47 ± 4.9 (25-58)
Waist-to-hip ratio (cm)	0.82 ± 0.05 (0.67-0.95)	0.83 ± 0.05 (0.71-0.92)	0.82 ± 0.05 (0.72-0.92)	0.83 ± 0.06 (0.70-0.99)	0.81 ± 0.06 (0.64-1.11)
Weight (kg)	62.4 ± 9.1 (38-90)	61.1 ± 11.1 (40-100)	59.6 ± 10.5 (43-102)	64.1 ± 10.4 (44-87)	59 ± 9.0 (37-98)
Body mass index (kg/m^2)	25.1 ± 3.5 (16.0-36.3)	24.7 ± 4.6 (13.8-42.2)	23.9 ± 3.3 (17.4-36.1)	25.9 ± 4.1 (18.0-34.4)	24.1 ± 3.6 (15.4-42.4)

*Childbearing women only.

Table 2. Comparison of physical activity variables by case-control status, SBCS, 1996-1998, % (*n*) or mean ± SD (range)

Variable	ER+/PR+	ER−/PR−	ER+/PR−	ER−/PR+	Controls
Premenopausal					
Adolescence (ages 13-19 y)					
Exercise (MET-hours/d/y)					
0	60 (208)	65 (120)	60 (43)	68 (49)	58 (571)
≤1.93	22 (76)	23 (42)	25 (18)	19 (14)	21 (211)
>1.93	18 (62)	12 (23)	15 (11)	13 (9)	21 (208)
Exercise (self-comparison)					
No exercise	60 (208)	65 (120)	60 (43)	68 (49)	58 (568)
About average or less	25 (87)	18 (33)	28 (20)	15 (11)	24 (238)
More than average	15 (50)	17 (32)	12 (9)	17 (12)	18 (180)
Exercise (sweating)					
No exercise/did not sweat	69 (237)	75 (139)	75 (54)	75 (54)	67 (665)
Sweated most/every time	31 (108)	25 (46)	25 (18)	25 (18)	33 (321)
Time spent in housework (hours a day)	1.6 ± 1.3 (0-7)	1.6 ± 1.4 (0-10)	1.7 ± 1.4 (0-6)	1.6 ± 1.3 (0-8)	1.6 ± 1.3 (0-8)
Time spent walking, nonoccupational (minutes a day)	54.6 ± 36.2 (0-240)	56.5 ± 31.8 (0-180)	60.0 ± 35.4 (10-240)	53.7 ± 29.0 (0-120)	54.1 ± 31.5 (0-210)
Last 10 y					
Exercise (MET-hours/d/y)					
0	89 (306)	89 (164)	82 (59)	88 (63)	85 (837)
≤0.87	7 (25)	7 (14)	10 (7)	11 (8)	9 (91)
>0.87	4 (15)	4 (7)	8 (6)	1 (1)	6 (62)
Exercise (self-comparison)					
No exercise	88 (305)	88 (162)	81 (58)	87 (63)	85 (837)
About average or less	9 (30)	8 (15)	12 (9)	7 (5)	10 (101)
More than average	3 (11)	4 (8)	7 (5)	6 (4)	5 (52)
Exercise (sweating)					
No exercise/did not sweat	92 (318)	93 (171)	93 (66)	94 (68)	90 (890)
Sweated most/every time	8 (27)	7 (12)	7 (5)	6 (4)	10 (100)
Time spent in housework (hours a day)	2.7 ± 1.3 (0-8)	2.8 ± 1.3 (0-7)	3.1 ± 1.4 (0-7)	2.7 ± 1.4 (1-9)	2.8 ± 1.4 (0-10)
Time spent walking, nonoccupational (minutes a day)	48.4 ± 46.9 (0-270)	47.7 ± 43.8 (0-210)	45.9 ± 39.0 (0-180)	43.1 ± 35.1 (0-180)	42.5 ± 37.6 (0-240)
Occupational sitting time*	39.6 ± 20.8 (0-108)	39.3 ± 20.6 (0-99)	40.0 ± 21.8 (0-105)	39.0 ± 18.7 (8-90)	35.7 ± 18.7 (0-114)
Lifetime occupational time spent walking (hours a day)	3.1 ± 2.6 (0-12)	2.9 ± 2.6 (0-10)	2.9 ± 2.7 (0-12)	3.3 ± 2.7 (0-8.2)	3.5 ± 2.6 (0-10)
Postmenopausal					
Adolescence (ages 13-19 y)					
Exercise (MET-hours/d/y)					
0	74 (136)	77 (57)	58 (21)	76 (25)	65 (370)
≤1.93	12 (22)	15 (11)	17 (6)	15 (5)	17 (95)
>1.93	14 (25)	8 (6)	25 (6)	9 (3)	18 (101)
Exercise (self-comparison)					
No exercise	74 (136)	77 (57)	58 (21)	76 (25)	65 (367)
About average or less	11 (19)	14 (10)	20 (7)	21 (7)	20 (113)
More than average	15 (28)	9 (7)	22 (8)	3 (1)	15 (83)
Exercise (sweating)					
No exercise/did not sweat	80 (147)	81 (60)	64 (23)	85 (28)	75 (421)
Sweated most/every time	20 (36)	19 (14)	36 (13)	15 (5)	25 (141)
Time spent in housework (hours a day)	1.9 ± 2.1 (0-10)	1.9 ± 1.8 (0-7)	1.7 ± 1.8 (0-7)	1.0 ± 1.2 (0-4)	2.1 ± 2.2 (0-13)
Time spent walking, nonoccupational (minutes a day)	52.1 ± 38.1 (0-240)	60.0 ± 47.0 (0-360)	60.6 ± 59.7 (0-300)	54.7 ± 30.2 (10-120)	64.1 ± 72.7 (0-780)
Last 10 y					
Exercise (MET-hours/d/y)					
0	69 (127)	80 (59)	78 (28)	58 (19)	58 (328)
≤0.87	18 (32)	15 (11)	3 (1)	18 (6)	19 (104)
>0.87	13 (24)	5 (4)	19 (7)	24 (8)	23 (131)
Exercise (self-comparison)					
No exercise	69 (127)	81 (60)	78 (28)	58 (19)	58 (326)
About average or less	24 (44)	12 (9)	14 (5)	30 (10)	32 (182)
More than average	7 (12)	7 (5)	8 (3)	12 (4)	10 (56)
Exercise (sweating)					
No exercise/did not sweat	84 (154)	92 (67)	89 (32)	73 (24)	76 (427)
Sweated most/every time	16 (29)	8 (6)	11 (4)	27 (9)	24 (136)
Time spent in housework (hours a day)	3.5 ± 1.6 (0-10)	4.0 ± 2.1 (0-10)	3.4 ± 1.9 (1-10)	3.2 ± 1.7 (0-7)	3.5 ± 1.6 (0-10)
Time spent walking, nonoccupational (minutes a day)	58.9 ± 41.2 (0-180)	58.6 ± 48.0 (0-300)	66.0 ± 52.9 (0-240)	48.8 ± 29.3 (0-120)	67.4 ± 54.0 (0-600)
Occupational sitting time*	57.2 ± 23.6 (1-111)	52.9 ± 26.4 (0-111)	51.3 ± 23.9 (15-102)	52.9 ± 22.2 (12-105)	51.3 ± 25.8 (0-133)
Lifetime occupational time spent walking (hours a day)	2.8 ± 2.6 (0-9.8)	3.5 ± 2.5 (0-8)	3.0 ± 3.1 (0-9.5)	3.5 ± 2.6 (0-8.3)	3.5 ± 2.8 (0-12.0)

*Sitting time calculated as sum of (sitting category for job classification × no. years on job) across all jobs.

activity on all tumor types, with this effect achieving statistical significance for several physical activity measures (MET-hours/d/y, sweating during exercise, and lifetime activity). Most notable is that premenopausal women who reported exercise in both adolescence and during the last 10 years showed a significant decreased risk by 66% for receptor-positive breast cancer and 49% for receptor-negative breast cancers. Given that power was limited among many of the strata due to small sample sizes, it is worth noting that many indices of physical activity (self-comparison and sweating during exercise) showed a marginally significant protective effect with all four breast cancer types. Because multiple significant associations were found between leisure-time activity and breast cancer type, we concluded that the overall pattern of association was similar for receptor-positive and receptor-negative breast cancers. Furthermore, the point estimates themselves were often very similar.

The homogeneity between tumor types was even more apparent among postmenopausal women (Table 4). Leisure-time physical activity in both adolescence and the last 10 years was protective for receptor-positive and negative breast cancers (ORs, 0.16-0.58). Additional exercise measures, such as self-comparison, sweating, and lifetime activity, showed a protective effect for three of the four tumor types. Activity in adolescence, the last 10 years, or both was protective for receptor-positive breast cancer with risk reductions ranging from 40% to 57%. Only activity in the last 10 years or during both adolescence and the last 10 years resulted in a reduction in risk by 62% to 79% for receptor-negative breast cancer. Activity in adulthood only was marginally associated with the ER+/PR− type. As with premenopausal women, activity was significantly associated with both receptor-positive and receptor-negative breast cancers. Interestingly, several significant associations were observed between some of the measures of activity (MET-hours/d/y, self-comparison, and sweating during exercise) and ER+/PR− breast cancer among postmenopausal women but not premenopausal women. Due to the greater number of significant associations, there was stronger evidence for homogeneity between receptor types among postmenopausal women.

The patterns of association for the groups were less consistent for occupational, household, and transportation-related activity (Tables 5 and 6). A statistically significant effect was only achieved for some measures of occupational and household activity. If one considers the associations that attained marginal significance, there seems to be greater consistency in pattern between the receptor-positive and the receptor-negative groups for occupational activity among premenopausal women. Overall, however, no consistent pattern of association is discernable.

Discussion

In this population of Chinese women, physical activity exposures were inversely associated with breast cancer regardless of receptor status. It should be noted that the association seemed to be less consistent across exposures for mixed receptor types. However, this may be a result of the small sample sizes in these groups. These findings suggest that physical activity may influence breast cancer risk, in part, through nonhormonal and more general pathways (e.g., insulin-related or growth factor–mediated pathways).

Results from this study are similar to those found by Enger et al. (33). Recreational physical activity was associated with a 30% to 60% reduction in risk for all tumor types when comparing the highest tertile with nonexercisers among premenopausal and postmenopausal women. When comparing numbers of subjects, it is worth noting that the present study had greater numbers of premenopausal breast cancers, whereas the Enger et al. study had a greater number of postmenopausal breast cancers. Both Lee et al. and Britton et al.

Table 3. Multivariable-adjusted relationships between hormone receptor-defined breast cancer and adolescent or adult leisure activity among premenopausal women, SBCS, 1996-1998

Variable	Controls (*n*)	ER+/PR+		ER−/PR−		ER+/PR−		ER−/PR+	
		n	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
Ages 13-19 y									
Exercise (MET-hours/d/y)									
0	571	208	1.00	120	1.00	43	1.00	49	1.00
≤1.93	211	76	1.00 (0.73-1.37)	42	0.98 (0.66-1.45)	18	1.14 (0.64-2.02)	14	0.79 (0.42-1.46)
>1.93	208	62	0.82 (0.59-1.14)	23	0.54* (0.33-0.87)	11	0.75 (0.38-1.49)	9	0.54† (0.26-1.11)
Exercise (self-comparison)									
No exercise	568	208	1.00	120	1.00	43	1.00	49	1.00
About average or less	238	87	1.03 (0.76-1.40)	33	0.70† (0.46-1.07)	20	1.15 (0.66-2.01)	11	0.54† (0.28-1.07)
More than average	180	50	0.74† (0.51-1.06)	32	0.82 (0.53-1.27)	9	0.68 (0.32-1.43)	12	0.83 (0.43-1.60)
Exercise (sweating)									
No exercise/did not sweat	665	237	1.00	139	1.00	54	1.00	54	1.00
Sweated most/every time	321	108	0.93 (0.71-1.22)	46	0.68* (0.47-0.98)	18	0.71 (0.41-1.23)	18	0.71 (0.41-1.24)
Last 10 y									
Exercise (MET-hours/d/y)									
0	837	306	1.00	164	1.00	59	1.00	63	1.00
≤0.87	91	25	0.69 (0.43-1.10)	14	0.71 (0.39-1.29)	7	1.05 (0.46-2.40)	8	1.16 (0.53-2.52)
>0.87	62	15	0.51* (0.27-0.95)	7	0.50† (0.22-1.13)	6	1.37 (0.56-3.34)	1	0.21 (0.03-1.57)
Exercise (self-comparison)									
No exercise	837	305	1.00	162	1.00	58	1.00	63	1.00
About average or less	101	30	0.69 (0.44-1.08)	15	0.66† (0.37-1.18)	9	1.25 (0.59-2.65)	5	0.65 (0.25-1.67)
More than average	52	11	0.51† (0.25-1.02)	8	0.77 (0.35-1.67)	5	1.36 (0.52-3.58)	4	1.01 (0.35-2.92)
Exercise (sweating)									
No exercise/did not sweat	890	318	1.00	171	1.00	66	1.00	68	1.00
Sweated most/every time	100	27	0.67† (0.42-1.05)	12	0.55† (0.29-1.04)	5	0.64 (0.25-1.64)	4	0.52 (0.18-1.47)
Lifetime activity									
Adolescent/adult									
No/no	517	186	1.00	110	1.00	35	1.00	46	1.00
Yes/no	320	120	1.05 (0.80-1.38)	54	0.80 (0.56-1.15)	24	1.14 (0.66-1.97)	17	0.62† (0.35-1.10)
No/yes	54	22	0.94 (0.55-1.61)	10	0.69 (0.34-1.43)	8	2.09† (0.90-4.84)	3	0.61 (0.18-2.07)
Yes/yes	99	18	0.44* (0.25-0.77)	11	0.51* (0.26-0.99)	5	0.76 (0.29-2.01)	6	0.69 (0.29-1.68)

NOTE: Adjusted for current age, age at first menarche, age at first birth, parity, and breast-feeding; each exercise variable represents a separate polytomous logistic model.
Abbreviation: 95% CI, 95% confidence interval.
*Ps ≤ 0.05.
†P > 0.05 and P ≤ 0.10.

Table 4. Multivariable-adjusted relationships between hormone receptor-defined breast cancer and adolescent or adult leisure activity among postmenopausal women, SBCS, 1996-1998

Variable	Controls (*n*)	ER+/PR+		ER−/PR−		ER+/PR−		ER−/PR+	
		n	OR (95% CI)	*n*	OR (95% CI)	*n*	OR* (95% CI)	*n*	OR (95% CI)
Ages 13-19 y									
Exercise (MMET-hours/d/y)									
0	370	136	1.00	57	1.00	21	1.00	25	1.00
≤1.93	95	22	0.58† (0.34-0.98)	11	0.77 (0.38-1.54)	6	1.05 (0.40-2.72)	5	0.77 (0.28-2.13)
>1.93	101	25	0.64* (0.39-1.05)	6	0.39† (0.16-0.93)	6	1.58 (0.69-3.64)	3	0.39 (0.11-1.34)
Exercise (self-comparison)									
No exercise	367	136	1.00	57	1.00	21	1.00	25	1.00
About average or less	113	19	0.40† (0.23-0.69)	10	0.57 (0.28-1.17)	7	1.01 (0.41-2.49)	7	0.90 (0.37-2.19)
More than average	83	28	0.90 (0.55-1.46)	7	0.56 (0.24-1.28)	8	1.73 (0.73-4.13)	1	0.16* (0.02-1.18)
Exercise (sweating)									
No exercise/did not sweat	421	147	1.00	60	1.00	23	1.00	28	1.00
Sweated most/every time	141	36	0.67* (0.34-1.03)	14	0.71 (0.38-1.31)	13	1.70 (0.82-3.49)	5	0.48 (0.18-1.29)
Last 10 y									
Exercise (MET-hours/d/y)									
0	328	127	1.00	59	1.00	28	1.00	19	1.00
≤0.87	104	32	0.76 (0.48-1.19)	11	0.56* (0.28-1.12)	1	0.10† (0.01-0.76)	6	0.94 (0.36-2.48)
>0.87	131	24	0.47† (0.29-0.77)	4	0.16† (0.06-0.47)	7	0.56 (0.22-1.41)	8	1.10 (0.46-2.67)
Exercise (self-comparison)									
No exercise	326	127	1.00	60	1.00	28	1.00	19	1.00
About average or less	182	44	0.60† (0.40-0.90)	9	0.26† (0.12-0.53)	5	0.25† (0.08-0.73)	10	0.90 (0.40-2.04)
More than average	56	12	0.55* (0.28-1.07)	5	0.48 (0.18-1.26)	3	0.59 (0.17-2.05)	4	1.38 (0.44-4.32)
Exercise (sweating)									
No exercise/did not sweat	427	154	1.00	67	1.00	32	1.00	24	1.00
Sweated most/every time	136	29	0.58† (0.37-0.90)	6	0.28† (0.12-0.65)	4	0.27† (0.08-0.91)	9	1.14 (0.51-2.56)
Lifetime activity									
Adolescent/adult									
No/no	228	98	1.00	46	1.00	16	1.00	16	1.00
Yes/no	100	29	0.60† (0.36-0.99)	13	0.66 (0.34-1.29)	12	1.54 (0.69-3.42)	12	1.02 (0.36-2.84)
No/yes	140	38	0.60† (0.38-0.93)	11	0.38† (0.19-0.76)	5	0.38* (0.12-1.19)	5	1.55 (0.66-3.63)
Yes/yes	95	18	0.43† (0.24-0.76)	4	0.21† (0.07-0.60)	3	0.42 (0.12-1.49)	2	0.35 (0.76-1.62)

NOTE: Adjusted for current age, age at first menarche, age at first birth, age at menopause, and breast-feeding; each exercise variable represents a separate polytomous logistic model.
*$P > 0.05$ and $P \leq 0.10$.
†Ps ≤ 0.05.

found no evidence for a differential effect of physical activity by receptor type either; however, the overall relationship between physical activity and breast cancer in these studies was null (28, 38). Furthermore, these studies only assessed recreational activity and had no estimates of occupational, household, or transportation-related activity as described in our investigation.

It is interesting to note that the effect of activity seemed to be modified by menopausal status as evidenced by the significance of the interaction term between some measures of activity and menopausal status. The protective effect seemed to be greater among postmenopausal women than premenopausal women. This suggests that the etiologic role of activity may differ by menopausal status. Alternatively, this may underscore possible differences in the composition of total daily physical activity by menopausal status. For example, occupational activity may comprise a greater proportion of total activity among premenopausal women, whereas household activity may contribute greater to total activity among postmenopausal women.

The results from this investigation provide important clues into the biological mechanism for the association between physical activity and breast cancer. If activity functioned solely through hormonal mechanisms, we would expect to see significant associations only among receptor-positive breast cancers. This has been shown previously for reproductive (i.e., hormone-related) risk factors that differentially associate with receptor-positive tumors cancer (7-16). The significant associations shown for receptor-negative cancers suggest that nonhormonal mechanisms may also play a role in the protective effect of activity.

Some animal studies provide clues that physical activity may act through nonhormonal mechanisms to affect breast cancer risk. In a study by Westerlind et al. (39), female Sprague-Dawley rats were exercised 30 minutes a day for 5 days a week starting at 28 days of age. A subset of animals was sacrificed at 28, 42, 56, 70, and 84 days. Sedentary rats were given a sham exercise protocol in which the animals were placed on the exercise wheel for the same duration. Although no carcinogen was given, changes in breast and other tissues were documented. No differences were noted between groups in relationship to growth, sexual maturation, steroid hormones, or number of mammary terminal end buds. This is in contrast to what might be expected if physical activity affected hormonal pathways alone. On the other hand, cellular proliferation and apoptosis in mammary tissues were increased significantly in the exercised animals. Westerlind et al. suggest that this might result in increased cellular turnover with quicker removal of preneoplastic cells. They also hypothesize that this same mechanism might lead to accelerated terminal differentiation of the mammary gland, effectively decreasing the period that cells would be susceptible to carcinogenic insult. It is worth reiterating that this study did not follow the animals for breast neoplasm development. However, to the extent that physical activity has shown an association with breast cancer risk in human studies, there is indirect evidence in animal studies that physical activity may have nonhormonal causal pathways to reduce breast cancer risk.

In addition to these cellular mechanisms, several other nonhormonal biological pathways have been proposed to explain the inverse association between physical activity and breast cancer (21). One such mechanism involves insulin-like growth factor-I (IGF-I). IGF-I is a potent stimulator of cell growth in *in vitro* studies. In human studies, a meta-analysis by Fletcher et al. found evidence for a positive association

Table 5. Multivariable-adjusted relationship between hormone receptor-defined breast cancer and occupational household, walking, or cycling activity among premenopausal women, SBCS, 1996-1998

Variable	Controls (*n*)	ER+/PR+		ER−/PR−		ER+/PR−		ER−/PR+	
		n	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
Occupational activity									
Sitting time*	976	342	1.00 (0.99-1.01)	185	1.00 (0.99-1.01)	72	1.00 (0.99-1.02)	72	1.00 (0.99-1.02)
Walking time (hours a day)	960	338	0.96 (0.91-1.01)	183	0.93 (0.87-0.99)	70	0.91† (0.83-1.01)	72	0.97 (0.89-1.07)
Activity self-rating‡	976	341	0.99 (0.99-1.00)	185	0.99 (0.98-1.00)	72	0.99 (0.98-1.01)	72	1.00 (0.99-1.01)
Average energy expenditure§	976	342	0.99§ (0.98-1.00)	185	0.99 (0.98-1.00‖)	72	0.98 (0.96-1.00‖)	72	1.01 (0.99-1.02)
Other activity									
Ages 13-19 y									
Household (hours a day)	975	341	0.96 (0.88-1.06)	185	0.99 (0.88-1.12)	72	1.05 (0.88-1.25)	72	0.97 (0.81-1.17)
Walking (minutes a day)	976	342	1.00 (0.99-1.00)	185	1.00 (1.00-1.01)	72	1.00 (1.00-1.01)	72	1.00 (0.99-1.01)
Last 10 y									
Household (hours a day)	975	342	0.91 (0.82-1.00‖)	185	0.99 (0.87-1.12)	72	1.14 (0.95-1.36)	72	0.92 (0.76-1.11)
Walking (minutes a day)	975	341	1.00† (1.00-1.01)	185	1.00 (1.00-1.01)	72	1.00 (1.00-1.01)	72	1.00 (0.99-1.01)

NOTE: Adjusted for current age, age at first menarche, age at first birth, parity, and breast-feeding; each exercise variable represents a separate polytomous logistic model.
*Sitting time calculated as sum of (sitting category for job classification × no. years on job) across all jobs.
†$P > 0.05$ and $P \leq 0.10$.
‡Activity self-rating calculated as sum of (activity category × no. years on job) across all jobs.
§Average energy expenditure calculated as sum of (energy expenditure category × no. years on job) across all jobs.
‖95% CI includes null, but Ps ≤ 0.05.

between IGF-I and IGF-I-binding protein-3 and breast cancer risk (40). Indeed, IGF-I has been found associated with increased risk for breast cancer in the very same population under study in this investigation (41). Physical activity has been found to decrease hyperinsulinemia and insulin resistance, which could result in decreased bioavailable IGF-I, thereby lowering breast cancer risk (42, 43). In this population of women, IGF-I levels decreased as age increased with higher levels observed among premenopausal women than among postmenopausal women (44), yet control subjects had lower levels of IGF-I in comparison with case subjects among both premenopausal and postmenopausal women. It is possible that the greater consistency of association between activity measures and breast cancer type (as evidenced by a greater number of significant associations) among postmenopausal women may be attributable, in part, to the chronic effects of physical activity on IGF-I levels.

Other hypothesized mechanisms involve increased immune surveillance (45). Up-regulation of natural killer cell numbers and activity and increased immune surveillance have been documented in athletes (46). Still, other mechanisms may involve a synergy between hormonal and nonhormonal mechanisms. In another study of the SBCS, the breast cancer risk estimate for women with both high estrone and IGF-I levels exceeded the estimate for either one of these biomarkers alone (47).

As with any epidemiologic study, there are potential limitations that should be noted. As is common with this type of research, the method of quantification of ER and PR status may not have been standard for all case participants. It is possible that different hormone receptor assay methods were used among cases. Hence, there may have been some misclassification of hormone receptor status. Although it is impossible to state with certainty, it is more likely that this type of misclassification would be nondifferential and would bias study findings toward a finding of no difference between receptor groups. Overall, the threat of this weakness to the validity of our central findings in this report is low; therefore, we believe our significant findings to be indicative of true relationships. It is also worth noting that ER and PR status was missing on 31% of the participants of the SBCS. To assess possible selection bias, we compared the cases included in the

Table 6. Multivariable-adjusted relationship between hormone receptor-defined breast cancer and occupational household, walking, or cycling activity among postmenopausal women, SBCS, 1996-1998

Variable	Controls (*n*)	ER+/PR+		ER−/PR−		ER+/PR−		ER−/PR+	
		n	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
Occupational activity									
Sitting time *	559	178	1.00 (1.00-1.01)	73	1.00 (0.99-1.01)	35	0.99 (0.98-1.01)	32	1.00 (0.98-1.01)
Walking time (hours a day)	553	176	0.91 (0.85-0.97)	72	1.00 (0.92-1.10)	35	0.94 (0.82-1.07)	32	1.03 (0.90-1.18)
Activity self-rating†	559	178	1.00 (0.99-1.00)	73	1.00 (0.99-1.01)	35	0.99 (0.98-1.01)	32	0.99 (0.97-1.01)
Average energy expenditure‡	559	178	1.00 (0.99-1.01)	73	1.00 (0.99-1.01)	35	1.00 (0.99-1.02)	32	1.00 (0.98-1.02)
Other activity									
Ages 13-19 y									
Household (hours a day)	559	177	0.98 (0.90-1.07)	73	0.96 (0.85-1.10)	35	0.90 (0.74-1.12)	32	0.69 (0.51-0.93)
Walking (minutes a day)	558	178	0.99 (0.99-1.00§)	72	1.00 (0.99-1.00)	35	1.00 (0.99-1.00)	32	1.00 (0.99-1.01)
Last 10 y									
Household (hours a day)	558	178	1.03 (0.93-1.15)	73	1.22 (1.07-1.40)	35	1.02 (0.82-1.27)	32	0.92 (0.72-1.18)
Walking (minutes a day)	559	178	1.00 (0.99-1.00)	73	1.00 (0.99-1.00)	35	1.00 (0.99-1.01)	32	0.99‖ (0.98-1.00)

NOTE: Adjusted for current age, age at first menarche, age at first birth, age at menopause, and breast-feeding; each exercise variable represents a separate polytomous logistic model.
*Sitting time calculated as sum of (sitting category for job classification × no. years on job) across all jobs.
†Activity self-rating calculated as sum of (activity category × no. years on job) across all jobs.
‡Average energy expenditure calculated as sum of (energy expenditure category × no. years on job) across all jobs.
§95% CI includes null, but Ps ≤ 0.05.
‖$P > 0.05$ and $P \leq 0.10$.

analysis with cases excluded due to missing information (data not shown). There were no statistical differences between the two groups for all the physical activity variables, except for occupational sitting time (cases included had a higher mean occupational sitting time than those excluded). Thus, we found no evidence for bias from the selection of cases for the analysis.

Among case-control studies are concerns of selection and recall bias. High participation rates for both cases (92%) and controls (90%) in this study minimized potential biases related to selection among controls. However, given that cases were interviewed at diagnosis or immediately afterward, the possibility exists that they may have reported their physical activity behaviors differently than controls. If cases believed that there was an inverse relationship between physical activity and breast cancer, they may have underreported their activity levels relative to controls. We are not able to evaluate this potential bias directly in this study; however, results from several prospective studies, which should be immune to recall biases, have reported inverse associations between physical activity and breast cancer (48-52). Regardless, this type of bias would most likely serve to influence measures of association toward a null finding, thereby strengthening the claim of a true association. Finally, the physical activity questionnaire employed in this research may not have provided a precise estimate of all levels and types of activities evaluated. It is well known that physical activity behaviors are measured with substantial error and nondifferential misclassification resulting from measurement error would function to attenuate any measures of association. A validation study examining the reliability and validity of a similar questionnaire (without an occupational activity assessment) found the majority of items used in this research to be sufficiently valid to stratify women into low and high activity levels (53).

This investigation also has many strengths. Although sample size has been proven to be limiting in some analyses, this is one of the largest studies of its kind, with one of the largest populations of receptor-negative breast cancers. A recently published study by Colditz et al. (54) included 2,096 breast cancer cases stratified by receptor type; however, no measures of physical activity were evaluated. Results obtained from this investigation confirm the findings of other studies and offer unique insights into the possible underlying biological mechanism(s) associating physical activity with breast cancer.

In conclusion, physical activity seemed to be inversely associated with breast cancer risk regardless of hormone receptor type. Similar patterns of association were shown between both receptor-positive and receptor-negative breast cancers. These findings need to be confirmed in other ethnic populations, such as Hispanic Americans and African Americans, who tend to have a higher rate of hormone-negative tumors (55), higher-risk tumors for a given stage (and concomitantly poorer survival; ref. 56), and very low rates of physical activity. (57) Additionally, future work should focus on the possible biological mechanisms of the physical activity/breast cancer association, including both hormonal and nonhormonal factors.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
2. Harris JR, Hellman S, Henderson IC, Kinne DW. Breast diseases. Philadelphia: J.B. Lippincott Co.; 1991.
3. Donegan WL. Prognostic factors. Stage and receptor status in breast cancer. Cancer 1992;70:1755–64.
4. Rayter Z. Steroid receptors in breast cancer. Br J Surg 1991;78:528–35.
5. Thorpe SM. Estrogen and progesterone receptor determinations in breast cancer. Technology, biology and clinical significance. Acta Oncol 1988;27:1–19.
6. Wittliff JL. Steroid-hormone receptors in breast cancer. Cancer 1984;53:630–43.
7. Hildreth NG, Kelsey JL, Eisenfeld AJ, et al. Differences in breast cancer risk factors according to the estrogen receptor level of the tumor. J Natl Cancer Inst 1983;70:1027–31.
8. Hislop TG, Coldman AJ, Elwood JM, Skippen DH, Kan L. Relationship between risk factors for breast cancer and hormonal status. Int J Epidemiol 1986;15:469–76.
9. Huang W-Y, Newman B, Millikan RC, et al. Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. Am J Epidemiol 2000;151:703–14.
10. Kreiger N, King WD, Rosenberg L, et al. Steroid receptor status and the epidemiology of breast cancer. Ann Epidemiol 1991;1:513–23.
11. McTiernan A, Thomas DB, Johnson LK, Roseman D. Risk factors for estrogen receptor-rich and estrogen receptor-poor breast cancers. J Natl Cancer Inst 1986;77:849–54.
12. Potter JD, Cerhan J, Sellers T, et al. Progesterone and estrogen receptors and mammary neoplasia in the Iowa Women's Health Study: how many kinds of breast cancer are there? Cancer Epidemiol Biomarkers Prev 1995;4:319–26.
13. Sellers TA, Vierkant RA, Cerhan JR, et al. Interaction of dietary folate intake, alcohol, and risk of hormone receptor-defined breast cancer in a prospective study of postmenopausal women. Cancer Epidemiol Biomarkers Prev 2002;11:1104–7.
14. Sellers TA, Davis J, Cerhan JR, et al. Interaction of waist/hip ratio and family history on the risk of hormone receptor-defined breast cancer in a prospective study of postmenopausal women. Am J Epidemiol 2002;155:225–33.
15. Yoo KY, Tajima K, Miura S, et al. Breast cancer risk factors according to combined estrogen and progesterone receptor status: a case-control analysis. Am J Epidemiol 1997;146:307–14.
16. Stanford JL, Szklo M, Boring CC, et al. A case-control study of breast cancer stratified by estrogen receptor status. Am J Epidemiol 1987;125:184–94.
17. Bauman AE. Updating the evidence that physical activity is good for health: an epidemiological review 2000-2003. Journal of Science & Medicine in Sport 2004;7:6–19.
18. Lee IM. Physical activity and cancer prevention-data from epidemiologic studies. Med Sci Sports Exerc 2003;35:1823–7.
19. Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. J Nutr 2002;132:3456S–64S.
20. Freidenreich CM. Physical activity and breast cancer risk: the effect of menopausal status. Exercise & Sport Sciences Reviews 2004;32:180–4.
21. McTiernan A, Ulrich C, Slate S, Potter J. Physical activity and cancer etiology: associations and mechanisms. Cancer Epidemiol Biomarkers Prev 1998;9:487–509.
22. Adams-Campbell LL, Rosenberg L, Rao RS, Palmer JR. Strenuous physical activity and breast cancer risk in African-American women. J Natl Med Assoc 2001;93:267–75.
23. Ainsworth BE, Sternfeld B, Slattery ML, Daguise V, Zahm SH. Physical activity and breast cancer. Cancer Suppl 1998;83:611–9.
24. 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.
25. Bernstein L. The roles of physical activity and electric blankets in breast cancer occurrence. Epidemiology 2001;12:598–600.
26. Breslow RA, Ballard-Barbash R, Munoz K, Graubard BI. Long-term recreational physical activity and breast cancer in the National Health and Nutrition Examination Survey I epidemiologic follow-up study. Cancer Epidemiol Biomarkers Prev 2001;10:805–8.
27. Lee IM, Paffenbarger RS. Physical activity and it relation to cancer risk: a prospective study of college alumni. Med Sci Sports Exerc 1994;26:831–7.
28. Lee IM, Rexrode KM, Cook NR, Hennekens CH, Burin JE. Physical activity and breast cancer risk: the Women's Health Study (United States). Cancer Epidemiol Biomarkers Prev 2001;12:137–45.
29. Marcus PM, Newman B, Moorman PG, et al. Physical activity at age 12 and adult breast cancer risk (United States). Cancer Causes Control 1999;10:293–302.
30. Matthews CE, Shu XO, Jin F, et al. Lifetime physical activity and breast cancer risk in the Shanghai Breast Cancer Study. Br J Cancer 2001;84:994–1001.
31. Oliveria SA, Christos PJ. The epidemiology of physical activity and cancer. Ann N Y Acad Sci 1997;833:79–90.
32. U.S. Department of Health and Human Services. Physical activity and health: a report of the Surgeon General. 11-37. 1996. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion.
33. Enger S, Ross R, Paganini-Hill A, Carpenter C, Bernstein L. Body size, physical activity, and breast cancer hormone receptor status: results from two case-control studies. Cancer Epidemiol Biomarkers Prev 2000;9:681–7.
34. Gao YT, Shu XO, Dai Q, et al. Association of menstrual and reproductive factors with breast cancer risk: results from the Shanghai Breast Cancer Study. Int J Cancer 2000;87:295–300.
35. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25:71–80.
36. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:S498–516.
37. McFadden D. Conditional logit analysis of qualitative choice behavior. In: Zarembka P, editor. Frontiers in econometrics. New York: Academic Press; 1974. p. 104–42.

38. Britton JA, Gammon MD, Schoenberg JB, et al. Risk of breast cancer classified by joint estrogen receptor and progesterone receptor status among women 20-44 years of age. Am J Epidemiol 2002;156:507 – 16.
39. Westerlind KC, McCarty HL, Gibson KJ, Strange R. Effect of exercise on the rat mammary gland: implications for carcinogenesis. Acta Physiol Scand 2002;175:147 – 56.
40. Fletcher O, Gibson L, Johnson N, et al. Polymorphisms and circulating levels in the insulin-like growth factor system and risk of breast cancer: a systematic review. Cancer Epidemiol Biomarkers Prev 2005; 14:2 – 19.
41. Yu H, Jin F, Shu XO, et al. Insulin-like growth factors and breast cancer risk in Chinese women. Cancer Epidemiol Biomarkers Prev 2002;11:705 – 12.
42. Mayer-Davis EJ, D'Agostino R, Karter AJ, et al. Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. J Clin Endocrinol Metab 1998;68:402 – 11.
43. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc Nutr Soc 2001;60:91 – 106.
44. Shephard RJ. Physical activity, training and the immune response. Carmel (IN): Cooper Publications; 1997.
45. Pedersen BKTN, Christensen LD, Klarlund K, Kragbak S, Halkjr-Kristensen J. Natural killer cell activity in peripheral blood of highly trained and untrained persons. Int J Sports Med 1989;10:129 – 31.
46. Yu H, Shu XO, Li BD, et al. Joint effect of insulin-like growth factors and sex steroids on breast cancer risk. Cancer Epidemiol Biomarkers Prev 2003;12: 1067 – 73.
47. Dorgan JF, Brown C, Barrett M, et al. Physical activity and risk of breast cancer in the Framingham Heart Study. Am J Epidemiol 1994;139:662 – 9.
48. McTiernan A, Kooperberg C, White E, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. JAMA 2003;290:1331 – 6.
49. Rockhill B, Willett WC, Hunter DJ, et al. A prospective study of recreational physical activity and breast cancer risk. Arch Intern Med 1999;159:2290 – 6.
50. Sesso HD, Paffenbarger RSJ, Lee IM. Physical activity and breast cancer risk in the College Alumni Health Study (United States). Cancer Causes Control 1998;9:433 – 9.
51. Thune I, Brenn T, Lund E, Gaard M. Physical activity and the risk of breast cancer. N Engl J Med 1997;336:1269 – 75.
52. Matthews CE, Shu XO, Yang G, et al. Reproducibility and validity of the Shanghai Women's Health Study physical activity questionnaire. Am J Epidemiol 2001;158:1114 – 22.
53. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl Cancer Inst 2004;96:218 – 28.
54. Gapstur SM, Dupuis J, Gann P, Collila S, Winchester DP. Hormone receptor status of breast tumors in Black, Hispanic, and non-Hispanic White women. An analysis of 13,239 cases. Cancer 1996;77:1465 – 71.
55. U.S. Cancer Statistics Working Group. United States cancer statistics: 2001 incidence and mortality. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2004.
56. Bolen JC, Rhodes L, Powell-Griner EE, Bland SD, Holtzman D. State-specific prevalence of selected health behaviors, by race and ethnicity—Behavioral Risk Factor Surveillance System, 1997. Morbidity Mortality Weekly Report 2000;49:1 – 60. CDC Surveillance Summaries.