Published OnlineFirst October 20, 2009; DOI: 10.1158/1055-9965.EPI-09-0538

Long-Term and Recent Recreational Physical Activity and Survival After Breast Cancer: The California Teachers Study

Carmen Nicole West-Wright,[1] Katherine DeLellis Henderson,[2] Jane Sullivan-Halley,[2] Giske Ursin,[1] Dennis Deapen,[1] Susan Neuhausen,[3] Peggy Reynolds,[4] Ellen Chang,[4] Huiyan Ma,[2] and Leslie Bernstein[1,2]

[1]Department of Preventive Medicine, Norris Comprehensive Cancer Center, University of Southern California Keck School of Medicine, Los Angeles, California; [2]Department of Population Sciences, Division of Cancer Etiology, City of Hope National Medical Center, Duarte, California; [3]School of Medicine, University of California, Irvine, California; and [4]Northern California Cancer Center, Fremont, California

Abstract

Introduction: **Long-term physical activity is associated with lower breast cancer risk. Little information exists on its association with subsequent survival.**
Methods: **California Teachers Study cohort members provided information in 1995-1996 on long-term (high school through age 54 years) and recent (past 3 years) participation in moderate and strenuous recreational physical activities. The 3,539 women diagnosed with invasive breast cancer after cohort entry and through December 31, 2004, were followed through December 31, 2005. Of these, 460 women died, 221 from breast cancer. Moderate and strenuous physical activities were combined into low (≤0.50 h/wk/y of any activity), intermediate (0.51-3.0 h/wk/y of moderate or strenuous activity but no activity >3.0 h/wk/y), or high activity (>3.0 h/wk/y of either activity type). Multivariable relative risks (RR) and 95% confidence intervals (95% CI) for mortality were estimated using Cox proportional hazards methods, adjusting for race/ethnicity, estrogen receptor status, disease stage, and baseline information on comorbidities, body mass index, and caloric intake.**
Results: **Women with high or intermediate levels of long-term physical activity had lower risk of breast cancer death (RR, 0.53; 95% CI, 0.35-0.80; and RR, 0.65; 95% CI, 0.45-0.93, respectively) than women with low activity levels. These associations were consistent across estrogen receptor status and disease stage, but were confined to overweight women. Deaths due to causes other than breast cancer were related only to recent activity.**
Conclusions: **Consistent long-term participation in physical activity before breast cancer diagnosis may lower risk of breast cancer death, providing further justification for public health strategies to increase physical activity throughout the lifespan.** (Cancer Epidemiol Biomarkers Prev 2009;18(11):2851–9)

Introduction

Physical inactivity is an acknowledged risk factor for breast cancer (1-12). The exact mechanism by which physical activity lowers breast cancer risk remains unclear, but may involve altering menstrual cycle characteristics (13), influencing age at menarche (14), or affecting body size (15, 16), all of which are associated with endogenous estrogen exposure. Other possible biological mechanisms linking physical activity and breast cancer risk include insulin sensitivity, immune function, and lipid peroxidation pathways (17-21).

The relationship of prediagnosis physical activity with survival after breast cancer is not as clearly defined as the association with breast cancer risk. Studies that examined the association between prediagnosis physical activity and survival after breast cancer in population-based patient series found no association (22, 23) or improved survival among women with higher physical activity levels (24, 25). Two studies, one of breast cancer diagnosed among members of a large cohort and the other of women recruited after diagnosis, reported that postdiagnosis physical activity levels were associated with increased survival (26, 27). To clarify whether physical activity earlier in life can have later benefits on breast cancer survival, we examined the association between long-term and recent prediagnosis recreational physical activity and survival after a diagnosis of invasive breast cancer among members of the California Teachers Study (CTS) cohort.

Materials and Methods

Study Participants. Detailed information on the development and follow-up of the CTS has been reported previously (28). In brief, the CTS is a prospective cohort study of 133,479 female public school teachers

Received 6/4/09; revised 8/10/09; accepted 8/31/09; published OnlineFirst 10/20/09.

Grant support: NIH [R01 CA 077398] and contract 97-10500 from the California Breast Cancer Research Fund. The funding sources did not contribute to the design or conduct of the study, nor to the writing or submission of this manuscript. The collection of cancer incidence data used in this study was supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract N01-PC-35136 awarded to the Northern California Cancer Center, contract N01-PC-35139 awarded to the University of Southern California, and contract N02-PC-15105 awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U55/CCR921930-02 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the authors. Endorsement by the State of California, Department of Health Services, the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

Requests for reprints: Leslie Bernstein, Department of Population Sciences, Division of Cancer Etiology, City of Hope National Medical Center, 1500 East Duarte Rd. Duarte, CA 91010. Phone: 626-471-7315; Fax: 626-471-7308. E-mail: LBernstein@coh.org

doi:10.1158/1055-9965.EPI-09-0538

Published OnlineFirst October 20, 2009; DOI: 10.1158/1055-9965.EPI-09-0538

Table 1. Age-adjusted percentage of selected baseline and disease characteristics for each level of long-term (strenuous plus moderate) recreational physical activity among women diagnosed with invasive breast cancer from 1995-2004 in the California Teachers Study

	Low, *n* (%)*	Intermediate, *n* (%)*	High, *n* (%)*
Race/ethnicity			
White	463 (85.3)	1,611 (90.5)	1,099 (91.4)
Non-white	76 (14.7)	175 (9.5)	115 (8.6)
BMI (kg/m^2)			
<25	275 (51.1)	969 (53.7)	701 (57.6)
25-29	154 (28.8)	503 (29.0)	316 (26.2)
≥30	73 (15.4)	252 (14.4)	144 (12.4)
Unknown	37 (4.7)	62 (3.0)	53 (3.9)
Total caloric intake (kcal)			
<1,271	181 (33.6)	554 (30.4)	326 (26.2)
1,271-1,682	145 (28.2)	529 (30.0)	373 (32.4)
>1,682	137 (26.6)	546 (31.8)	419 (34.0)
Unknown	76 (11.6)	157 (7.9)	96 (7.3)
Estrogen receptor status			
Positive	385 (71.2)	1,283 (72.0)	881 (73.0)
Negative	70 (14.1)	245 (14.0)	135 (10.9)
Unknown	84 (14.7)	258 (14.0)	198 (16.2)
Number of comorbid conditions†			
0	360 (69.7)	1,376 (77.7)	934 (77.4)
1	147 (25.7)	362 (19.8)	246 (19.9)
≥2	32 (4.6)	48 (2.5)	34 (2.8)
Disease stage‡			
Localized	366 (66.1)	1,207 (67.2)	864 (71.5)
Nonlocalized	169 (33.2)	562 (32.0)	343 (27.9)
Unknown	4 (0.6)	17 (0.8)	7 (0.6)

NOTE: All assessments were completed at baseline prior to breast cancer diagnosis.
*Age-adjusted percents presented.
†Based on self-reported personal history of stroke, heart attack/myocardial infarction, diabetes and high blood pressure.
‡Nonlocalized includes regional and metastatic disease.

and administrators who were current or retired public school professionals and members of the California State Teachers Retirement System at the time the study began in 1995. Women joined the cohort by completing a detailed, mailed questionnaire in 1995-1996.

Women were considered eligible for this analysis if they were California residents at baseline and had an incident first primary invasive breast cancer diagnosis after joining the cohort. Incident cases of invasive breast cancer (International Classification of Disease Oncology topography codes ICD9-174, ICD10-C50) were identified through annual linkages of the CTS database with the California Cancer Registry, a state-mandated population-based cancer registry that records information on >99% of incident cancers diagnosed in California. Overall, 3,588 CTS participants who were living in California at baseline were diagnosed with a first primary invasive breast cancer after joining the cohort and before January 1, 2005. We limited the study to the 3,542 breast cancer patients who provided complete questionnaire information on physical activity and history of comorbid conditions. Three additional women were excluded whose deaths were due to an external cause of death (e.g. accident), producing an analytic cohort of 3,539 women.

Measurement of Follow-up. Follow-up began on the date of breast cancer diagnosis and continued to death (n = 460) or the end of the follow-up period on December 31, 2005, whichever occurred earlier. By restricting the study to patients who were diagnosed through December 31, 2004, we ensured that all patients had the opportunity for at least 1 year of follow-up after diagnosis. The entire cohort was followed through annual newsletters, three follow-up questionnaires, annual linkage with the United States Postal Service National Change of Address database, and change-of-address postcards submitted by participants. Deaths were ascertained through linkages with the California State Mortality Files, the Social Security Administration Death Master File, and the National Death Index. For all deaths, date and cause of death were recorded. We obtained cause of death from death certificates for the 460 total deaths included in these analyses (221 breast cancer deaths; 69 deaths from other types of cancer including 12 lung cancers, 8 ovarian cancers and 4 brain tumors; 68 cardiovascular disease deaths; 38 cerebrovascular disease deaths; 28 cardiopulmonary or pulmonary disease deaths; 4 diabetes deaths; 3 thrombosis deaths; and 29 deaths from other causes). We did not review cause of death through secondary means.

Measures of Recreational Physical Activity. Detailed information on recreational physical activity was collected in the baseline questionnaire. Participants provided information on recreational physical activity for two intensity levels, strenuous and moderate, at each of six time intervals (during high school, between the ages of 18-24, 25-34, 35-44 and 45-54 years, and during the past 3 years). Long-term physical activity was defined for this analysis as reported activities from high school through age 54 (or the participant's age at entry if younger than 54). Recent physical activity was defined for this analysis as reported activity within the 3 years prior to cohort entry. Examples of strenuous exercise included running, jogging, swimming laps, racquetball, aerobics, calisthenics, and cycling on hills. Examples of moderate intensity exercise included brisk walking, golf, softball, volleyball, recreational tennis, and cycling on flat surfaces. For each intensity level and time period, participants reported the

Published OnlineFirst October 20, 2009; DOI: 10.1158/1055-9965.EPI-09-0538

average number of hours per week (categories: none, 0.5, 1, 1.5, 2, 3, 4-6, 7-10, and ≥11) and the average number of months per year (categories: 1-3, 4-5, 7-9, and 10-12) that they engaged in such activities. For each intensity level and time period, we calculated the average hours per week per year by multiplying hours per week by months per year and dividing by 12 mo. The actual value, or when appropriate the midpoint value, of the category range was used to make this calculation. A value of 12 was used when the average number of hours per week was ≥11. In this way we calculated the average hours per week for each year of age from age 15 through 54 years or through the age at cohort entry if the woman was <54 years of age. We then summed across all eligible years and calculated the average annual hours per week of long-term recreational physical activity for each intensity level. Average annual long-term strenuous recreational physical activity and average annual long-term moderate recreational physical activity were then categorized into four quartiles (≤0.50, 0.51-1.50, 1.51-3.00, >3.00 h/wk/y). Two variables that combined moderate activity and strenuous activity were created, one for long-term activity and one for recent activity; each was classified as low, intermediate, or high average weekly hours per year of recreational physical activity. Women were classified in the low long-term recreational activity category when both average annual long-term strenuous and average annual long-term moderate recreational physical activity were in the lowest category (≤0.50 h/wk/y). Women were classified in the intermediate long-term recreational activity category when either strenuous or moderate long-term recreational activity fell in the second or third quartile (0.51-3.00 h/wk/y) and neither strenuous long-term recreational activity nor moderate long-term recreational activity was in the highest quartile (>3.00 h/wk/y). Women were classified in the high long-term recreational activity category when either strenuous long-term recreational activity or moderate long-term recreational activity was >3.00 h/wk/y. The measure for recent activity at baseline (within the last 3 years) was created in a similar fashion. A combined moderate and strenuous activity variable to test the possible importance of changes in recreational physical activity by age (before and after age 25 years) was created (activity <30 min/wk/y both before and after age 25 years, activity ≥30 min/wk/y before age 25 years but <30 min/wk/y after age 25 years, activity <30 min/wk/y before age 25 years but activity ≥30 min/wk/y after age 25 years, and activity ≥30 min/wk/y in both age periods).

Assessment of Breast Cancer Risk Factors. The baseline questionnaire provided information on factors that

Table 2. Selected baseline and disease characteristics and multivariable relative risks with 95% confidence intervals for the association between the characteristics and death by cause among women diagnosed with invasive breast cancer from 1995-2004 in the California Teachers Study

	Total (n = 3,539)	Breast cancer deaths (n = 221)	RR* (95% CI)	All causes of death† (n = 460)	RR* (95% CI)
Age (years)					
Mean (SD)	58.9 (11.75)	-	-	-	-
Range	26-94				
	n (%)	n (%)		n (%)	
Race/ethnicity					
White	3,173 (89.7)	199 (90.0)	1.00	417 (90.7)	1.00
Non-white	366 (10.3)	22 (10.0)	0.87 (0.55-1.39)	43 (9.3)	1.02 (0.74-1.43)
BMI (kg/m^2)					
<25	1,945 (55.0)	99 (44.8)	1.00	220 (47.8)	1.00
25-29	973 (27.5)	61 (27.6)	1.16 (0.83-1.62)	119 (25.9)	0.98 (0.78-1.24)
≥30	469 (13.2)	39 (17.6)	1.71 (1.16-2.53)	72 (15.7)	1.42 (1.08-1.88)
Unknown	152 (4.3)	22 (10.0)	2.51 (1.51-4.15)	49 (10.7)	1.61 (1.14-2.27)
Total caloric intake (kcal)					
<1,271	1,061 (30.0)	78 (35.3)	1.00	160 (34.8)	1.00
1,271-1,682	1,047 (29.6)	49 (22.2)	0.67 (0.46-0.97)	121 (26.3)	0.85 (0.67-1.09)
>1,682	1,102 (31.1)	68 (30.8)	0.79 (0.56-1.11)	111 (24.1)	0.75 (0.58-0.97)
Unknown	329 (9.3)	26 (11.8)	1.01 (0.63-1.64)	68 (14.9)	1.06 (0.78-1.44)
Estrogen receptor status					
Positive	2,549 (72.0)	122 (55.2)	1.00	300 (65.2)	1.00
Negative	450 (12.7)	59 (26.7)	2.88 (2.08-3.99)	80 (17.4)	1.71 (1.32-2.22)
Unknown	540 (15.3)	40 (18.1)	1.38 (0.94-2.03)	80 (17.4)	1.05 (0.80-1.38)
Number of comorbid conditions‡					
0	2,670 (75.4)	162 (73.3)	1.00	281 (61.1)	1.00
1	755 (21.3)	45 (20.4)	0.82 (0.58-1.16)	143 (31.1)	1.29 (1.04-1.60)
≥2	114 (3.2)	14 (6.3)	1.46 (0.81-2.64)	36 (7.8)	1.72 (1.18-2.50)
Disease stage§					
Localized	2,437 (68.9)	65 (29.4)	1.00	244 (53.0)	1.00
Nonlocalized	1,074 (30.3)	153 (69.2)	5.75 (4.24-7.78)	206 (44.8)	2.67 (2.19-3.25)
Unknown	28 (0.8)	3 (1.4)	3.28 (0.97-11.11)	10 (2.2)	2.37 (1.14-4.93)

NOTE: All assessments were completed at baseline.
*All models are stratified by age (in years) and adjusted for race, BMI, total caloric intake, estrogen receptor status, number of comorbid conditions, stage and physical activity summary variable.
†Includes breast cancer and other causes of death: cancers other than breast cancer (69), cardiovascular disease (68), cerebrovascular disease (38), thrombosis (3), cardiopulmonary and pulmonary diseases (28), diabetes (4), and other (29).
‡Based on self-reported personal history of stroke, heart attack/myocardial infarction, diabetes and high blood pressure.
§Nonlocalized includes regional and metastatic disease.

Published OnlineFirst October 20, 2009; DOI: 10.1158/1055-9965.EPI-09-0538

Table 3. Multivariable relative risk and 95% confidence interval for the association between physical activity prior to diagnosis and death by cause among women diagnosed with invasive breast cancer from 1995-2004 in the California Teachers Study

Physical activity group	Death due to breast cancer (n = 221)	Death due to any cause other than breast cancer (n = 239)	Death due to any cause (n = 460)
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Long-term physical activity Combined*			
Low	1.00	1.00	1.00
Intermediate	0.65 (0.45-0.93)	0.98 (0.69-1.38)	0.83 (0.65-1.07)
High	0.53 (0.35-0.80)	0.91 (0.62-1.34)	0.73 (0.55-0.96)
P trend†	0.003	0.63	0.03
Recent physical activity Combined*			
Low	1.00	1.00	1.00
Intermediate	1.17 (0.84-1.65)	0.76 (0.56-1.03)	0.89 (0.71-1.11)
High	1.08 (0.73-1.58)	0.61 (0.42-0.88)	0.78 (0.60-1.02)
P trend†	0.69	0.007	0.06

NOTE: All models are stratified by age in years and adjusted for race, BMI, total caloric intake, number of comorbid conditions, and estrogen receptor status.
*Long-term strenuous and moderate activity summary variable classifies women with no activity >0.5 h/wk/y activity into the low group, those with at least one of moderate or strenuous activity >3 h/wk/y into the high group, and all others, that is, those with some activity that is >0.5 h/wk/y and ≤3 h/wk/y but not >3 h/wk/y into the intermediate group.
†P trend is the log-relative risk across categories (1, 2, and 3) of the strenuous-moderate summary variable.

were considered pertinent to breast cancer risk, including race/ethnicity, personal and family history of breast cancer, dietary intake, weight and height, history of a comorbid disease, and exogenous hormone use (28).

Body mass index (BMI; weight at baseline in kilograms divided by the squared value of height at baseline in meters, kg/m^2) was categorized into four groups: <25, 25-29.99, ≥30 kg/m^2, or unknown. Total caloric intake at baseline was assessed using the 1995 validated version of the Block food-frequency questionnaire (29). At baseline, we collected information on personal history of diabetes, high blood pressure, heart attack/myocardial infarction and stroke; each comorbidity variable was categorized as yes or no. We created a summary comorbidity variable reflecting the number of these conditions reported, and categorized this variable into three groups: none, 1 or ≥2.

Data on tumor estrogen receptor status, tumor progesterone receptor status, and summary stage of disease at diagnosis were obtained from California Cancer Registry records. Stage of breast cancer at diagnosis was summarized as localized (n = 2,437) or nonlocalized (n = 1,074); nonlocalized included regional (n = 1,008) and metastatic (n = 66) disease. Information on disease stage was missing for 28 women.

Statistical Analysis. We considered three end points: death from breast cancer, death from all causes other than breast cancer, and death from all causes combined. Cox proportional hazards regression models were fit separately for each end point to assess the relative risk (RR) of death associated with a woman's physical activity prior to diagnosis. Each hazard rate ratio, presented as a RR with a 95% confidence interval (95% CI), was estimated using age in days at diagnosis and age in days at event or censoring time to define the start and end of follow-up. In the primary analysis, death from breast cancer was the end point; women who died from other causes were censored at the date of death. In the analysis with all causes of death other than breast cancer as the outcome, patients who died of breast cancer were censored at the date of death. Multivariable models were used to evaluate the associations between each measure of physical activity and survival. Models were stratified by age at diagnosis in years and adjusted for race/ethnicity (white versus non-white), BMI, total caloric intake, history of comorbid diseases, estrogen receptor and progesterone receptor status, and stage of breast cancer at diagnosis. We conducted tests for trend in the RR across physical activity categories by fitting the median value for each activity level as a continuous variable in the age-stratified, multivariable model. We also examined the effect of physical activity on breast cancer survival according to stage and estrogen receptor status. Women with unknown stage were placed in the nonlocalized category when adjusting for stage, but were excluded from models stratified by stage.

We first fit each comorbid condition individually and then replaced these by the three-category comorbid condition variable described above. As these two approaches fit the data equally well, we present only the latter results. Further we initially adjusted for receptor status using a five-category variable (estrogen receptor positive and progesterone receptor positive, estrogen receptor positive and progesterone receptor negative, estrogen receptor negative and progesterone receptor positive, estrogen receptor negative and progesterone receptor negative, or at least one receptor status unknown). As the results for the more extensively adjusted model were similar to those for a model that adjusted only for estrogen receptor status, we present results for the simplified model. We assessed whether BMI modified any association between physical activity and breast cancer survival by constructing a likelihood ratio test that assessed homogeneity of trends between normal-weight (<25 kg/m^2) and overweight (≥25 kg/m^2) women.

Kaplan-Meier survival curves plotted for each activity group were used to check the proportional hazards assumption; no violations were observed. We repeated each analysis excluding women who died within 1 year of diagnosis (n = 58), and the results were consistent with those that included all deaths; we present the results of analyses based on all women. We also restricted the

Published OnlineFirst October 20, 2009; DOI: 10.1158/1055-9965.EPI-09-0538

analysis to women who were not missing BMI; again, the results were consistent with those that are presented. We also examined the effects of using the date of breast cancer diagnosis and date of last follow-up as the time metric for the Cox proportional hazards regression; the results were similar to those using age as the time metric, and we present the latter. P values of ≤0.05 were considered statistically significant; tests for trend utilized two-sided P values. All analyses were done using SAS version 9.1 (SAS Institute, Cary, North Carolina).

Results

Table 1 presents the age-adjusted percentages for selected baseline and disease characteristics of the 3,539 invasive breast cancer patients in our analytic cohort stratified by the combined long-term physical activity variable. White women were more likely to participate in high levels of activity compared with non-white women. Women in the high-activity group were more likely to be lean than women in the low or intermediate groups. They were also more likely to consume more calories and have estrogen receptor–positive tumors. Women with two or more comorbid conditions were more likely to be in the low-activity group compared with women in the high-activity group and more likely to have nonlocalized stage of disease.

Table 2 presents the baseline and disease characteristics and the relative risk associated with survival. The mean age at diagnosis was 58.9 years (range, 26-94 years). The majority of women (89.7%) were white. Fifty-five percent of patients had a BMI <25 kg/m^2 at baseline, with few (13.2%) classified as obese (≥30 kg/m^2). Of the breast cancer patients with known estrogen receptor status, 72.0% had estrogen receptor–positive tumors, which accounted for 55.2% of the breast cancer deaths during follow-up and 65.2% of the deaths due to any cause. Overall, 21.3% of patients reported at least one comorbid condition; 111 reported a history of diabetes, 776 reported a history of high blood pressure, 55 reported a history of a heart attack, and 51 reported a history of a stroke at baseline. Among women who died from any cause, 31.1% reported a history of at least one of these comorbid conditions. The majority of breast cancer patients (68.9%) were diagnosed with localized disease, but the majority of breast cancer deaths (69.2%) occurred among women with more advanced disease. The overall 5-year survival probability was 88.5 (95% CI, 87.3-89.7). The median follow-up time among women who died from any cause (n = 460) was 38.5 months. The median follow-up time among women who did not die during the study period (n = 3079) was 64.0 months.

Obesity (BMI ≥30 kg/m^2) was significantly associated with higher risk of death due to breast cancer (RR, 1.71; 95% CI, 1.16-2.53), as was having an estrogen receptor–negative tumor (RR, 2.88; 95% CI, 2.08-3.99; Table 2). Comorbid conditions were also associated with greater risk of death from all causes. Having at least one comorbid condition was associated with a higher risk of death due to any cause; a statistically nonsignificant association between comorbidity and risk of breast cancer death was observed only among women with two or more comorbid conditions. Advanced stage of disease at diagnosis was statistically significantly associated with increased risk of dying from breast cancer and of dying from any cause; the RR for breast cancer death was nearly 6-fold greater (RR, 5.75; 95% CI, 4.24-7.78) for women with advanced disease than for women with localized disease.

Risk of breast cancer death was inversely associated with combined moderate and strenuous long-term recreational physical activity (Table 3). Women in the intermediate long-term activity category had 35% lower risk of breast cancer death (RR, 0.65; 95% CI, 0.45-0.93), and those in the high long-term activity category had 47% reduced risk of breast cancer death (RR, 0.53; 95% CI, 0.35-0.80), compared with women in the low category (i.e., inactive women; P trend = 0.003). Recent recreational physical activity prior to diagnosis was not strongly related to the risk of breast cancer death.

Table 4. Multivariable relative risk and 95% confidence interval for the association between physical activity and death by cause according to estrogen receptor status among women in the California Teachers Study

Physical activity (h/wk/y)	Breast cancer deaths (n = 221)		Death due to any cause (n = 460)	
	ER positive (n = 2,549)	ER negative (n = 450)	ER positive (n = 2,549)	ER negative (n = 450)
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Long-term physical activity Combined*				
Low	1.00	1.00	1.00	1.00
Intermediate	0.66 (0.41-1.06)	0.42 (0.19-0.95)	0.85 (0.63-1.17)	0.47 (0.25-0.91)
High	0.46 (0.26-0.80)	0.33 (0.13-0.83)	0.78 (0.56-1.11)	0.33 (0.15-0.74)
P trend†	0.007	0.03	0.18	0.008
Recent physical activity Combined*				
Low	1.00	1.00	1.00	1.00
Intermediate	1.13 (0.71-1.80)	0.87 (0.42-1.80)	0.97 (0.73-1.29)	0.65 (0.35-1.22)
High	1.06 (0.62-1.81)	1.18 (0.51-2.74)	0.89 (0.64-1.23)	0.71 (0.35-1.46)
P trend†	0.83	0.77	0.49	0.26

NOTE: All models are stratified by age in years and adjusted for race, BMI, total caloric intake, number of comorbid conditions and estrogen receptor status.
Abbreviation: ER, estrogen receptor.
*Long-term strenuous and moderate activity summary variable classifies women with no activity >0.5 h/wk/y activity into the low group, those with at least one of moderate or strenuous activity >3 h/wk/y into the high group, and all others, that is, those with some activity that is >0.5 h/wk/y and ≤3 h/wk/y but not >3 h/wk/y into the intermediate group.
†P trend is the log-relative risk across categories (1, 2 and 3) of the strenuous-moderate summary variable.

Published OnlineFirst October 20, 2009; DOI: 10.1158/1055-9965.EPI-09-0538

Table 5. Adjusted relative risks of death due to breast cancer among women in the California Teachers Study, by long-term combined strenuous and moderate physical activity, for baseline body mass index as a possible effect modifier

		Long-term combined moderate and strenuous physical activity*			P trend	$P_{homogeneity}$
		Low	Intermediate	High		
		RR (95% CI)	RR (95% CI)	RR (95% CI)		
BMI[†]	Breast cancer deaths					
<25 kg/m^2	99	1.0	1.24 (0.65 -2.36)	1.15 (0.58 -2.29)	0.81	0.03
≥25 kg/m^2	100	1.0	0.52 (0.32 -0.86)	0.41 (0.23 -0.74)	0.004	
BMI[‡]	Deaths due to any cause					
<25 kg/m^2	220	1.0	0.89 (0.62-1.29)	0.83 (0.55-1.25)	0.37	0.60
≥25 kg/m^2	191	1.0	0.79 (0.54-1.16)	0.70 (0.46-1.08)	0.12	

NOTE: All models are stratified by age in years and adjusted for race, BMI, total caloric intake, number of comorbid conditions, and estrogen receptor status.
*Long-term strenuous and moderate activity summary variable classifies women with no activity >0.5 h/wk/y activity into the low group, those with at least one of moderate or strenuous activity >3 h/wk/y into the high group, and all others, that is, those with some activity that is >0.5 h/wk/y and ≤3 h/wk/y but not >3 h/wk/y into the intermediate group.
[†]There were 22 cases excluded due to missing BMI.
[‡]There were 130 cases excluded due to missing BMI.

We did not observe an association between increasing long-term recreational physical activity and lower risk of death due to all causes other than breast cancer (Table 3). However, we observed a 39% reduction in risk of death from causes other than breast cancer for women in the high category of recent combined moderate and strenuous activity (RR, 0.61; 95% CI, 0.42-0.88; P trend = 0.007).

The results for analyses of death due to all causes were similar to those for death due to breast cancer (Table 3). The combined long-term activity variable was inversely associated with decreasing risk of death due to all causes (P trend = 0.03). For recent physical activity, increases in the combined activity variable were only modestly associated with decreases in risk of death (P trend = 0.06).

Although the total numbers of breast cancer deaths in women with estrogen receptor–positive breast cancer (122 deaths) and estrogen receptor–negative breast cancer (59 deaths) were small (Table 2), we detected a statistically significant inverse association between long-term combined activity and risk of breast cancer death in patients with estrogen receptor–positive tumors (P trend = 0.007) and in patients with estrogen receptor–negative tumors (P trend = 0.03; Table 4). Recent combined activity was not associated with risk of breast cancer death among patients with either estrogen receptor–positive or estrogen receptor–negative breast cancer.

Among women with estrogen receptor–negative breast cancers, a statistically significant inverse association was observed between long-term combined activity and risk of death from any cause (P trend = 0.008). No association was observed for estrogen receptor–positive breast cancers. Recent combined activity was not associated with risk of death due to any cause among patients regardless of their estrogen receptor subtype.

BMI significantly modified the association between long-term combined recreational physical activity and risk of death due to breast cancer. Among overweight women (BMI ≥25 kg/m^2), risk of death due to breast cancer was decreased in both the intermediate (RR, 0.52; 95% CI, 0.32-0.86) and high (RR, 0.41; 95% CI, 0.23-0.74) physical activity categories (P trend = 0.004; Table 4). By contrast, among normal-weight women (BMI <25 kg/m^2) risk of death due to breast cancer was not associated with long-term combined moderate and strenuous recreational physical activity (P trend = 0.81; P homogeneity of trends = 0.03; Table 5). Further, BMI did not significantly modify the association between long-term combined recreational physical activity and risk of death due to any cause. We examined risk of breast cancer death and all causes of death in relation to recreational physical activity levels before age 25 years and from age 25 years to age 54 years (or current age if younger than 54 years). Women who were physically active at either age showed the same reductions in risk as women who were active at both ages (data not shown).

Increasing long-term combined moderate and strenuous recreational physical activity was associated with decreasing risk of death due to breast cancer, regardless of disease stage (P trend = 0.008 for localized disease and P trend = 0.04 for advanced disease; Table 6). Increased recent combined moderate and strenuous physical activity was associated with a decreasing risk of death due to any cause other than breast cancer (P trend = 0.04) for women with advanced disease.

Discussion

We found different associations of recreational physical activity prior to breast cancer diagnosis with risk of death, depending on timing of activity and cause of death. An intermediate or high level of long-term recreational physical activity was associated with a lower risk of dying of breast cancer overall, but only among women with a BMI of ≥25 kg/m^2. Recent activity levels at entry did not influence the risk of breast cancer death, nor did changes in activity levels by age (before and after 25 years). In contrast, recent activity levels were associated with a lower risk of dying from non–breast cancer causes, but long-term activity levels were not.

Two prior population-based studies of breast cancer patients reported no association between prediagnosis lifetime physical activity and breast cancer survival (22, 23). However, a study of young women with breast cancer found a positive association (24), as did a study with premenopausal and postmenopausal women (25).

Published OnlineFirst October 20, 2009; DOI: 10.1158/1055-9965.EPI-09-0538

Protective effects of postdiagnosis physical activity have been reported in three studies (26, 27, 30). In the Nurses' Health Study of female registered nurses, physical activity measured two to three years after diagnosis was associated with reduced overall and reduced breast cancer–specific mortality (26). These results were recently replicated in a population-based, multiethnic cohort of breast cancer patients identified after diagnosis (30). Among patients who participated in an earlier population-based study, recreational physical activity measured after breast cancer diagnosis was likewise associated with reduced mortality from breast cancer (27). Both our study and one recently published by Friedenreich and colleagues (25) report on cumulative long-term physical activity prior to diagnosis and breast cancer survival. Our results and those of Friedenreich provide comparable risk estimates for long-term and lifetime exercise activity. Friedenreich and colleagues reported no evidence of effect modification by other factors. However, we observed evidence of effect modification by BMI, with an inverse association between long-term strenuous and moderate physical activity and risk of breast cancer death among overweight women only. This result may be explained by the suppressive effects of physical activity on estrogen (31), insulin, and insulin-like growth factor levels (32), particularly in overweight women, among whom circulating levels of hormones such as estrogen are higher than in normal-weight women (33).

Among the strengths of this study are its prospective study design and the identification and confirmation of cancer diagnoses through the California Cancer Registry. We also obtained detailed information on recreational physical activity throughout most of a woman's life, collected prior to breast cancer diagnosis; this allowed us to assess and compare the effects of both long-term and recent physical activity.

Previous studies have suggested that routine physical activity levels decline below prediagnosis levels in the first year after breast cancer diagnosis, but return within three years to prediagnosis levels (34, 35). It is unclear why long-term prediagnosis activity, but not recent prediagnosis activity, influenced survival in our study. The relatively short three-year time period for recent activity may not represent a woman's usual pattern over her entire lifetime as accurately as the long-term activity measure does. Using the three-category physical activity measure (low, intermediate, and high moderate and strenuous activity), we found that 56% of the breast cancer patients were classified the same for long-term and recent activity. Further, we speculate that women who engage in recreational physical activity throughout their lives prior to breast cancer diagnosis will be more likely to resume this activity after recovery from the effects of surgery and treatment as was shown in two recent studies (34, 35).

Our results regarding long-term prediagnosis recreational physical activity are compatible with those from both the Nurses' Health Study and the Collaborative Women's Longevity Study, which suggest that physical activity after breast cancer diagnosis increases survival (26, 27). However, given our observation of a relatively marked reduction in risk of breast cancer death for women in the intermediate long-term activity category, which is similar to the risk reduction for women in the high-activity category, we cannot rule out the possibility that inactive women may differ from active women in other ways that increase their risk of breast cancer death, but not their risk of death due to other causes. Among the women with incident breast cancer we found that less active women had higher total daily caloric intake and were more likely to have comorbid conditions than less active patients; these factors were included as covariates in the analyses.

In these data, recent recreational physical activity was inversely associated with risk of death due to all non–breast cancer causes and death due to any

Table 6. Multivariable relative risk and 95% confidence interval for the association between physical activity and death by cause according to stage of breast cancer at diagnosis among women in the California Teachers Study

Physical activity (h/wk/y)	Breast cancer deaths (n = 221)		Death due to any cause (n = 460)		Death due to any cause other than breast cancer (n = 239)	
	Localized (n = 2,437)	Nonlocalized* (n = 1,074)	Localized (n = 2,437)	Nonlocalized* (n = 1,074)	Localized (n = 2,437)	NonLocalized* (n = 1,074)
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Long-term physical activity Combined†						
Low	1.00	1.00	1.00	1.00	1.00	1.00
Intermediate	0.48 (0.25-0.92)	0.74 (0.46-1.17)	0.80 (0.57-1.13)	0.85 (0.57-1.27)	0.88 (0.58-1.31)	1.39 (0.59-3.29)
High	0.35 (0.17-0.73)	0.57 (0.34-0.96)	0.75 (0.51-1.09)	0.66 (0.42-1.05)	0.92 (0.60-1.44)	0.89 (0.33-2.43)
P trend‡	0.008	0.04	0.15	0.07	0.78	0.74
Recent physical activity Combined†						
Low	1.00	1.00	1.00	1.00	1.00	1.00
Intermediate	0.83 (0.44-1.55)	1.31 (0.85-2.02)	0.86 (0.63-1.17)	1.03 (0.71-1.47)	0.89 (0.62-1.28)	0.54 (0.26-1.13)
High	0.94 (0.48-1.83)	1.09 (0.67-1.79)	0.75 (0.53-1.08)	0.84 (0.55-1.29)	0.69 (0.45-1.06)	0.38 (0.15-0.98)
P trend‡	0.85	0.71	0.12	0.45	0.09	0.04

NOTE: All models are stratified by age in years and adjusted for race, BMI, total caloric intake, number of comorbid conditions and estrogen receptor status.
*Nonlocalized stage of disease includes 1,008 regional and 66 metastatic; 28 women with unknown disease state were excluded from these stage specific analyses.
†Long-term strenuous and moderate activity summary variable classifies women with no activity >0.5 h/wk/y activity into the low group, those with at least one of moderate or strenuous activity >3 h/wk/y into the high group, and all others, that is, those with some activity that is >0.5 h/wk/y and ≤3 h/wk/y but not >3 hr/wk/y into the intermediate group.
‡P trend is the log-relative risk across categories (1, 2 and 3) of the strenuous-moderate summary variable.

Published OnlineFirst October 20, 2009; DOI: 10.1158/1055-9965.EPI-09-0538

cause. It is possible that this does not reflect a causal association but rather results from temporal ambiguity, as we cannot show effectively that the exposure preceded the outcome. Recent physical activity likely represents overall general health; women who are not feeling well may exercise less, thereby creating a noncausal association between physical activity and health status.

We have previously reported that long-term strenuous recreational physical activity was inversely associated with risk of estrogen receptor–negative but not estrogen receptor–positive breast cancer (12). Here we found that higher levels of long-term recreational physical activity prior to diagnosis were associated with improved survival independent of estrogen receptor subtype. Long-term physical activity was also associated with improved survival, independent of disease stage in this study, despite the small number of deaths ($n = 65$) in the group of women with localized disease.

This study was limited by a lack of data on household physical activity, which may have hindered our ability to fully assess a woman's total activity profile. We also lacked information on occupational activity; however, we would not expect prediagnosis occupational activity levels to vary substantially, because women in the cohort were employed in a relatively homogeneous range of occupations, typically public school teacher or other public school professional, for most of their adult years. One study has shown that total lifetime occupational and household activity does not have an impact on survival or risk of recurrence, progression or new primary, and that recreational activity is associated with increased survival (25). Therefore, if occupational levels did vary, we would not anticipate such variation to have a substantial impact on our results. Finally, although we did not abstract medical records, and therefore lack information on treatment and follow-up care, we have found similar effects of recreational activity on survival as have studies controlling for such factors (25) and, as noted above, our results do not vary by estrogen receptor status or stage at diagnosis. Further, we are confident that participants had health insurance, as they were public school professionals. By controlling for age, stage of disease, and estrogen receptor status, we have provided some control for any potential differences in treatment and follow-up care.

In summary, we have found that increased long-term recreational physical activity prior to breast cancer diagnosis is associated with a decreased risk of death due to breast cancer. This finding provides further evidence that an increased level of recreational physical activity over the lifetime, whether strenuous or moderate, has a beneficial effect on breast cancer outcome. Combined with previous findings suggesting that postdiagnosis physical activity improves breast cancer survival, our results support the implementation of strategies and programs to increase physical activity among girls and women of all ages, both before and, if necessary, after the onset of breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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.

We thank the CTS Steering Committee who are responsible for the formation and maintenance of the cohort within which this study was conducted but are not included as authors on the current paper: Hoda Anton-Culver, Christina A. Clarke, Rosemary Cress, Pamela L. Horn-Ross, Joan Largent, Rich Pinder, Daniel O. Stram, Dee W. West, and Argyrios Ziogas.

References

1. 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.
2. Bernstein L, Henderson BE, Hanisch R, Sullivan-Halley J, Ross RK. Physical exercise and reduced risk of breast cancer in young women. J Natl Cancer Inst 1994;86:1403–8.
3. Friedenreich CM, Rohan TE. Physical activity and risk of breast cancer. Eur J Cancer Prev 1995;4:145–51.
4. D'Avanzo B, Nanni O, La Vecchia C, et al. Physical activity and breast cancer risk. Cancer Epidemiol Biomarkers Prev 1996;5:155–60.
5. Coogan PF, Newcomb PA, Clapp RW, Trentham-Dietz A, Baron JA, Longnecker MP. Physical activity in usual occupation and risk of breast cancer. Cancer Causes Control 1997;8:626–31.
6. Fraser GE, Shavlik D. Risk factors, lifetime risk, and age at onset of breast cancer. Ann Epidemiol 1997;7:375–82.
7. Thune I, Brenn T, Lund E, Gaard M. Physical activity and the risk of breast cancer. N Engl J Med 1997;336:1269–75.
8. Sesso HD, Paffenbarger RS, Jr., Lee IM. Physical activity and breast cancer risk in the College Alumni Health Study. Cancer Cause Control 1998;9:433–9.
9. Lee IM, Rexrode KM, Cook NR, Hennekens CH, Burin JE. Physical activity and breast cancer risk: the Women's Health Study. Cancer Causes Control 2001;12:137–45.
10. Vainio H, Bianchini F. Weight control and physical activity. Lyon: IARC Press; 2002.
11. 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.
12. Dallal CM, Sullivan-Halley J, Ross RK, et al. Long-term recreational physical activity and risk of invasive and *in situ* breast cancer: the California Teachers Study. Arch Intern Med 2007;167:408–15.
13. Bernstein L, Ross RK, Lobo RA, Hanisch R, Krailo MD, Henderson BE. The effects of moderate physical activity on menstrual cycle patterns in adolescence: implications for breast cancer prevention. Br J Cancer 1987;55:681–5.
14. Merzenich H, Boeing H, Wahrendorf J. Dietary fat and sports activity as determinants for age at menarche. Am J Epidemiol 1993; 138:217–24.
15. Irwin ML, Yasui Y, Ulrich CM, et al. Effect of exercise on total and intra-abdominal body fat in postmenopausal women: a randomized controlled trial. JAMA 2003;289:323–30.
16. Astrup A. Physical activity and weight gain and fat distribution changes with menopause: current evidence and research issues. Med Sci Sports Exerc 1999;31:S564–7.
17. Hoffman-Goetz L, Apter D, Demark-Wahnefried W, Goran MI, McTiernan A, Reichman ME. Possible mechanisms mediating an association between physical activity and breast cancer. Cancer 1998;83: 621–8.
18. McTiernan A, Ulrich C, Slate S, Potter J. Physical activity and cancer etiology: associations and mechanisms. Cancer Causes Control 1998;9: 487–509.
19. Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. J Nutr 2002;132: 3456S–64S.
20. Endogenous Hormones Breast Cancer Collaborative Group. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst 2003;95:1218–26.
21. Gago-Dominguez M, Jiang X, Castelao JE. Lipid peroxidation, oxidative stress genes and dietary factors in breast cancer protection: a hypothesis. Breast Cancer Res 2007;9:201.
22. Rohan TE, Fu W, Hiller JE. Physical activity and survival from breast cancer. Eur J Cancer Prev 1995;4:419–24.
23. Enger SM, Bernstein L. Exercise activity, body size and premenopausal breast cancer survival. Br J Cancer 2004;90:2138–41.
24. Abrahamson PE, Gammon MD, Lund MJ, et al. Recreational physical

Published OnlineFirst October 20, 2009; DOI: 10.1158/1055-9965.EPI-09-0538

activity and survival among young women with breast cancer. Cancer 2006;107:1777–85.
25. Friedenreich CM, Gregory J, Kopciuk KA, Mackey JR, Courneya KS. Prospective cohort study of lifetime physical activity and breast cancer survival. Int J Cancer 2009;124:1954–62.
26. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. JAMA 2005; 293:2479–86.
27. Holick CN, Newcomb PA, Trentham-Dietz A, et al. Physical activity and survival after diagnosis of invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2008;17:379–86.
28. Bernstein L, Allen M, Anton-Culver H, et al. High breast cancer incidence rates among California teachers: results from the California Teachers Study. Cancer Causes Control 2002;13:625–35.
29. Horn-Ross PL, Hoggatt KJ, West DW, et al. Recent diet and breast cancer risk: the California Teachers Study. Cancer Causes Control 2002;13:407–15.
30. Irwin ML, Smith AW, McTiernan A, et al. Influence of pre- and post-diagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. J Clin Oncol 2008; 26:3958–64.
31. Schmitz KH, Lin H, Sammel MD, et al. Association of physical activity with reproductive hormones: the Penn Ovarian Aging Study. Cancer Epidemiol Biomarkers Prev 2007;16:2042–7.
32. Irwin ML, Varma K, Alvarez-Reeves M, et al. Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale Exercise and Survivorship study. Cancer Epidemiol Biomarkers Prev 2009;18:306–13.
33. Key TJ, Allen NE, Verkasalo PK, Banks E. Energy balance and cancer: the role of sex hormones. Proc Nutr Soc 2001;60:81–9.
34. Kendall AR, Mahue-Giangreco M, Carpenter CL, Ganz PA, Bernstein L. Influence of exercise activity on quality of life in long-term breast cancer survivors. Qual Life Res 2005;14:361–71.
35. Irwin ML, McTiernan A, Bernstein L, et al. Physical activity levels among breast cancer survivors. Med Sci Sports Exerc 2004;36: 1484–91.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Long-Term and Recent Recreational Physical Activity and Survival After Breast Cancer: The California Teachers Study

Carmen Nicole West-Wright, Katherine DeLellis Henderson, Jane Sullivan-Halley, et al.

Cancer Epidemiol Biomarkers Prev 2009;18:2851-2859. Published OnlineFirst October 20, 2009.