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Long-term and recent recreational physical activity and survival after breast cancer: the California Teachers Study

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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 hr/wk/yr of any activity), intermediate (0.51–3.0 hr/wk/yr of moderate or strenuous activity but no activity >3.0 hr/wk/yr) or high activity (>3.0 hr/wk/yr of either activity type). Multivariable relative risks (RR) and 95% confidence intervals (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 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.

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

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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 pre-diagnosis 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 pre-diagnosis 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 post-diagnosis 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 pre-diagnosis recreational physical activity and survival after a diagnosis of invasive breast cancer among members of the California Teachers Study (CTS) cohort.

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 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 more than 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 cause of death was 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=463) 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 one year of follow-up after diagnosis. The entire cohort has been 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 three 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 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 months. 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 less than 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 hr/wk/yr). 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 hr/wk/yr). 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 hr/wk/yr) and neither strenuous long-term recreational activity nor moderate long-term recreational activity was in the highest quartile (>3.00 hr/wk/yr). 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 hr/wk/yr. 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/yr both before and after age 25 years, activity ≥30 min/wk/yr before age 25 years but <30 min/wk/yr after age 25 years, activity <30 min/wk/yr before age 25 years but activity ≥30 min/wk/yr after age 25 years, and activity ≥30 min/wk/yr in both age periods).

Assessment of Breast Cancer Risk Factors

The baseline questionnaire provided information on factors that 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 [kg] divided by the squared value of height at baseline in meters [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; categorizing this variable into three groups: none, 1 or ≥2.

Data on tumor estrogen receptor (ER) status, tumor progesterone receptor (PR) 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 non-localized (n=1,074); non-localized included regional (n=1,008) and metastatic (n=66) disease. Information on disease stage was missing for 28 women.

Statistical Analysis

We considered three endpoints: 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 endpoint 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 baseline 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 endpoint; 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 baseline in years and adjusted for race (white versus non-white), BMI, total caloric intake, history of comorbid diseases, ER and PR 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 ER status. Women with unknown stage were placed in the non-localized 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 (ER-positive and PR-positive, ER-positive and PR-negative, ER-negative and PR-positive, ER-negative and PR-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 ER 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 one 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 analysis to women who were not missing BMI and again, 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 or less were considered statistically significant; tests for trend utilized two-sided P values. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

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 to non-white women. Women in the high activity group were more likely to be lean then women in the low or intermediate groups. They were also more likely to consume more calories and have ER-positive tumors. Women with two or more comorbid conditions were more likely to be in the low activity group compared to women in the high activity group and more likely to have non-localized 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. 55.0% of patients had a BMI less than 25 kg/m^2 at baseline, with few (13.2%) classified as obese (≥30 kg/m^2). 72.0% of the breast cancer patients with known ER status had ER-positive tumors. ER-positive tumors 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 five-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 ER-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 non-significant 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 six-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 to 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.

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).

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 ER-positive breast cancer (122 deaths) and ER-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 ER-positive tumors (p-trend= 0.007) and in patients with ER-negative tumors (p-trend=0.03, Table 4). Recent combined activity was not associated with risk of breast cancer death among patients with either ER-positive or ER-negative breast cancer.

Among women with ER-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 ER-positive breast cancers. Recent combined activity was not associated with risk of death due to any cause among patients regardless of their ER 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 $\geq$ 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 (Table 6, p-trend=0.008 for localized disease and p-trend=0.04 for advanced disease). 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 physical activity was associated with a lower risk of dying of breast cancer overall, but only among women with a BMI of at least 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 pre-diagnosis 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). Protective effects of post-diagnosis 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 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 pre-diagnosis levels in the first year after breast cancer diagnosis, but return within three years to pre-diagnosis levels (34,35). It is unclear why long-term pre-diagnosis activity, but not recent pre-diagnosis 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 pre-diagnosis 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 co-morbid 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 cause. It is possible that this does not reflect a causal association but rather results from temporal ambiguity, as we cannot demonstrate 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 non-causal association between physical activity and health status.

We have previously reported that long-term strenuous recreational physical activity was inversely associated with risk of ER-negative but not ER-positive breast cancer (12). Here we found that higher levels of long-term recreational physical activity prior to diagnosis were associated with improved survival irrespective of ER 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 pre-diagnosis occupational activity levels to vary substantially, since 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 affects of recreational activity on survival as studies that controlling for such factors (25) and, as noted above, our results do not vary by ER status or stage at diagnosis. Further, we are confident that participants had health insurance, since they were public school professionals. By controlling for age, stage of disease and ER 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 post-diagnosis 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.

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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 (%)[a]	Intermediate (%)[a]	High (%)[a]
Race/ethnicity			
White	463 (85.3)	1611 (90.5)	1099 (91.4)
Non-white	76 (14.7)	175 (9.5)	115 (8.6)
Body Mass Index (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)			
<1271	181 (33.6)	554 (30.4)	326 (26.2)
1271–1682	145 (28.2)	529 (30.0)	373 (32.4)
> 1682	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)	1283 (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[b]			
0	360 (69.7)	1376 (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[c]			
Localized	366 (66.1)	1207 (67.2)	864 (71.5)
Non-localized	169 (33.2)	562 (32.0)	343 (27.9)
Unknown	4 (0.6)	17 (0.8)	7 (0.6)

[a] Age-adjusted percents presented.

[b] Based on self-reported personal history of stroke, heart attack/myocardial infarction, diabetes and high blood pressure.

[c] Non-localized includes regional and metastatic disease.

[d] Note: All assessments were completed at baseline prior to breast cancer diagnosis.

Table 2

Selected baseline and disease characteristics and multivariable relative risks (RR) with 95% confidence intervals (CI) 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=3539 (%)	Breast Cancer Deaths N=221 (%)	RR[a] (95% CI)	All Causes of Death[b] N=460 (%)	RR[a] (95% CI)
Age					
Mean (SD)	58.9 (11.75)	-	-	-	-
Range	26–94				
Race/ethnicity					
White	3173 (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)
Body Mass Index (kg/m^2)					
< 25	1945 (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)					
<1271	1061 (30.0)	78 (35.3)	1.00	160 (34.8)	1.00
1271–1682	1047 (29.6)	49 (22.2)	0.67 (0.46–0.97)	121 (26.3)	0.85 (0.67–1.09)
> 1682	1102 (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	2549 (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[c]					
0	2670 (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[d]					
Localized	2437 (68.9)	65 (29.4)	1.00	244 (53.0)	1.00
Non-localized	1074 (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)

[a] All models are stratified by age (in years) and adjusted for race, body mass index, total caloric intake, estrogen receptor status, number of comorbid conditions, stage and physical activity summary variable.

[b] 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).

[c] Based on self-reported personal history of stroke, heart attack/myocardial infarction, diabetes and high blood pressure.

[d] Non-localized includes regional and metastatic disease.

[e] Note: All assessments were completed at baseline.

Table 3

Multivariable relative risk (RR) and 95% confidence interval (CI) 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 Groups	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)
Long-term Physical Activity			
Combined[a]			
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[b]	0.003	0.63	0.03
Recent Physical Activity			
Combined[a]			
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[b]	0.69	0.007	0.06

[a] Long-term strenuous and moderate activity summary variable classifies women with no activity >0.5 hr/wk/yr activity into the low group, those with at least one of moderate or strenuous activity >3 hr/wk/yr into the high group, and all others, that is those with some activity that is >0.5 hr/wk/yr and ≤ 3 hr/wk/yr but not activity greater than 3 hr/wk/yr into the intermediate group.

[b] P trend is the log-relative risk across categories (1, 2 and 3) of the strenuous-moderate summary variable. All models are stratified by age in years and adjusted for race, body mass index, total caloric intake, number of comorbid conditions and estrogen receptor status.

Table 4

Multivariable relative Risk (RR) and 95% confidence interval (CI) for the association between physical activity and death by cause according to estrogen receptor (ER) status among women in the California Teachers Study

	Breast Cancer Deaths (N=221)		Death due to any Cause (N=460)	
Physical Activity (h/wk/y)	**ER Positive (N=2549) RR (95% CI)**	**ER Negative (N=450) RR (95% CI)**	**ER Positive (N=2549) RR (95% CI)**	**ER Negative (N=450) RR (95% CI)**
Long-term Physical Activity				
Combined[a]				
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[b]	0.007	0.03	0.18	0.008
Recent Physical Activity				
Combined[a]				
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[b]	0.83	0.77	0.49	0.26

[a] Long-term strenuous and moderate activity summary variable classifies women with no activity >0.5 hr/wk/yr activity into the low group, those with at least one of moderate or strenuous activity >3 hr/wk/yr into the high group, and all others, that is those with some activity that is >0.5 hr/wk/yr and ≤ 3 hr/wk/yr but not activity greater than 3 hr/wk/yr into the intermediate group.

[b] P trend is the log-relative risk across categories (1, 2 and 3) of the strenuous-moderate summary variable. All models are stratified by age in years and adjusted for race, body mass index, total caloric intake, number of comorbid conditions and estrogen receptor status.

Table 5

Adjusted[a] 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[b]			P_{trend}	$P_{homogeneity}$
		Low	Intermediate	High		
Body Mass Index[c]	**Breast Cancer Deaths**					
< 25 kg/m^2	99	1.0 (reference)	1.24 (0.65 – 2.36)	1.15 (0.58 – 2.29)	0.81	0.03
≥ 25 kg/m^2	100	1.0 (reference)	0.52 (0.32 – 0.86)	0.41 (0.23 – 0.74)	0.004	
Body Mass Index[d]	**Deaths due to any Cause**					
< 25 kg/m^2	220	1.0 (reference)	0.89 (0.62–1.29)	0.83 (0.55–1.25)	0.37	0.60
≥ 25 kg/m^2	191	1.0 (reference)	0.79 (0.54–1.16)	0.70 (0.46–1.08)	0.12	

[a] All models are stratified by age in years and adjusted for race, body mass index, total caloric intake, number of comorbid conditions and estrogen receptor status.

[b] Long-term strenuous and moderate activity summary variable classifies women with no activity >0.5 hr/wk/yr activity into the low group, those with at least one of moderate or strenuous activity >3 hr/wk/yr into the high group, and all others, that is those with some activity that is >0.5 hr/wk/yr and ≤ 3 hr/wk/yr but not activity greater than 3 hr/wk/yr into the intermediate group.

[c] 22 cases are excluded due to missing body mass index

[d] 130 cases are excluded due to missing body mass index

Table 6

Multivariable relative risk (RR) and 95% confidence interval (CI) 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

	Breast Cancer Deaths (N=221)		Death due to any Cause (N=460)		Death due to any Cause Other than Breast Cancer (N=239)	
Physical Activity (h/wk/y)	**Localized (N=2437) RR (95% CI)**	**Non-Localized[a] (N= 1074) RR (95% CI)**	**Localized (N=2437) RR (95% CI)**	**Non-Localized[a] (N= 1074) RR (95% CI)**	**Localized (N=2437) RR (95% CI)**	**Non-Localized[a] (N= 1074) RR (95% CI)**
Long-term Physical Activity						
Combined[b]						
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[c]	0.008	0.04	0.15	0.07	0.78	0.74
Recent Physical Activity						
Combined[b]						
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[c]	0.85	0.71	0.12	0.45	0.09	0.04

[a] Non-local stage of disease includes: 1008 regional and 66 metastatic; 28 women with unknown disease state were excluded from these stage specific analyses.

[b] Long-term strenuous and moderate activity summary variable classifies women with no activity >0.5 hr/wk/yr activity into the low group, those with at least one of moderate or strenuous activity >3 hr/wk/yr into the high group, and all others, that is those with some activity that is >0.5 hr/wk/yr and ≤ 3 hr/wk/yr but not activity greater than 3 hr/wk/yr into the intermediate group

[c] P trend is the log-relative risk across categories (1, 2 and 3) of the strenuous-moderate summary variable. All models are stratified by age in years and adjusted for race, body mass index, total caloric intake, number of comorbid conditions and estrogen receptor status.