Published in final edited form as:
*Cancer Epidemiol Biomarkers Prev*. 2009 January ; 18(1): 87–95. doi:10.1158/1055-9965.EPI-08-0595.

# Physical Activity and Risk of Recurrence and Mortality in Breast Cancer Survivors: Findings from the LACE Study

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## Abstract

**Introduction—**Identifying modifiable factors that reduce the risk of recurrence and improve survival in breast cancer survivors is a pressing concern. The purpose of this study was to examine the association of physical activity following diagnosis and treatment with the risk of breast cancer recurrence and mortality and all-cause mortality in women with early-stage breast cancer.

**Materials and Methods—**The sample consisted of 1,970 women from the Life After Cancer Epidemiology study, a prospective investigation of behavioral risk factors and health outcomes. Self-reported frequency and duration of work-related, household and caregiving, recreational, and transportation-related activities during the six months prior to enrollment were assessed. Outcomes were ascertained from electronic or paper medical charts. Hazard ratios and 95% confidence intervals were estimated from delayed entry Cox proportional hazards models.

**Results—**Although age-adjusted results suggested that higher levels of physical activity were associated with reduced risk of recurrence and breast cancer mortality (*P* for trend = 0.05 and 0.07, respectively for highest versus lowest level of hours per week of moderate physical activity), these associations were attenuated after adjustment for prognostic factors and other confounding variables (*P* for trend = 0.36 and 0.26). In contrast, a statistically significant protective association between physical activity and all-cause mortality remained in multivariable analyses (hazard ratio, 0.66; 95% confidence interval, 0.42–1.03; *P* for trend = 0.04).

**Conclusions—**These findings do not support a protective effect of physical activity on breast cancer recurrence or mortality but do suggest that regular physical activity is beneficial for breast cancer survivors in terms of total mortality.

## Introduction

More than two million women living in the United States today have been diagnosed with and treated for breast cancer, and new cases develop at an annual rate of approximately 129.1 per 100,000 (1). Because the breast cancer mortality rate (25.8 per 100,000 per year) has declined substantially in recent years (2), the cohort of breast cancer survivors has grown steadily. As a result, questions about longer-term health and well-being have emerged as critical concerns for both the survivors themselves and the scientific and clinical communities. Of particular interest is the identification of modifiable factors, such as



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**Disclosure of Potential Conflicts of Interest**
No potential conflicts of interest were disclosed.

physical activity, that may contribute to lower rates of breast cancer–related morbidity and improved quality of life as well as overall survival.

Over 60 cohort and case-control studies have examined the role of physical activity in the primary prevention of breast cancer (3). Although the evidence is not entirely consistent, the findings suggest a reasonably clear, modest risk reduction of about 20% to 30% for active women compared with sedentary women (4, 5). The decreased risk seems greater for postmenopausal women than for premenopausal women; a meta-analysis conducted by the WHO in 2004 concluded that the relative risk associated with inactivity was 1.25 (95% confidence interval, 1.20–1.30) for women ages 15 to 44 years, and 1.34 (95% confidence interval, 1.29–1.39) for women ages 45 to 69 years (6). A recent "best evidence" review found strong support for a 20% to 80% risk reduction among postmenopausal women and suggested that for each additional hour per week of physical activity, the risk of breast cancer incidence decreased by 6% (7). Exactly how much and what type of physical activity is necessary to achieve this risk reduction, and at what points in the lifespan the level of activity is most influential, remain unknown, although another recent review of the literature found stronger relations for recreational activity, vigorous activity, and lifetime or later-life activity (8).

Whether or not physical activity has a role in the secondary prevention of breast cancer, or is associated with improved overall survival, as is true in the population at large (9, 10), is not well established. An early case-control study by Rohan and Hiller (11) found no association between physical activity assessed prior to diagnosis and either all-cause or breast cancer mortality, whereas a recent population-based cohort study of women with a history of breast cancer found an inverse association between prediagnosis physical activity and all-cause mortality (12), but only in women who were overweight or obese at the time of diagnosis. Another study of prediagnosis physical activity and survival in premenopausal women found only a weak, statistically nonsignificant association for recent activity and no association for lifetime activity (13).

To date, the most compelling evidence to suggest that physical activity after diagnosis and treatment is associated with reduced risk of breast cancer recurrence and/or improved survival comes from three cohort studies. In the Nurses' Health Study (14), women who participated in at least 9 metabolic equivalent (MET)-hours a week of physical activity had a 25% to 50% risk reduction in recurrence, breast cancer mortality, and total mortality, an association that was particularly apparent in women with hormone-responsive tumors. A similar decrease in risk of both all-cause and breast cancer mortality was also observed in the Collaborative Women's Longevity Study (15), and in the Health, Eating, Activity and Lifestyle study (16) there was a reduced risk of all-cause mortality. Physical activity was also associated with reduced risk of death in the Women's Healthy Eating and Lifestyle study, but only in women who also consumed >5 fruits and vegetables a day (17).

The purpose of the current study was to examine further how physical activity following breast cancer diagnosis and treatment influences recurrence and survival. Specifically, we addressed this question with a detailed, comprehensive measure of physical activity that encompassed both recreational and nonrecreational domains, using data from the Life After Cancer Epidemiology (LACE) study, a prospective, observational investigation of behavioral risk factors and health outcomes in women diagnosed with early-stage breast cancer.

# Materials and Methods

## Study Sample

The sample for this study consisted of 1,970 women in the LACE cohort who completed a physical activity questionnaire. Details of the sampling and recruitment procedures for LACE have been previously published (18). Briefly, the sampling frame consisted of women; ages 18 to 79 y; diagnosed with stage I (≥1 cm), II, or IIIa breast cancer from 1997 to 2000 in either the Kaiser Permanente Northern California Cancer Registry or the Utah Cancer Registry; who were diagnosed within 39 mo of enrollment; had completed cancer treatment; and were free of any documented recurrence. In addition to the Kaiser Permanente and Utah cancer registries, the sampling frame included 883 women screened and eligible for the Women's Healthy Eating and Lifestyle study, a dietary intervention trial examining the prevention of breast cancer recurrence. These women had declined participation in the Women's Healthy Eating and Lifestyle study but met the eligibility requirements specified above. Of the 5,656 women in the sampling frame who were identified as meeting the entry criteria, 2,586 (45.7%) completed initial enrollment. Subsequent review to confirm eligibility resulted in 298 exclusions, leaving 2,288 women in the cohort, 82% of whom came from Kaiser Permanente, 12% from Utah, and 6% from Women's Healthy Eating and Lifestyle. Based on Kaiser Permanente Cancer Registry data, those who enrolled were similar to those who did not in terms of disease characteristics but were more likely to be age >50 y (19). For the current analysis, an additional 14% ($n$ = 318) were excluded because of missing physical activity questionnaires, leaving a final sample size of 1,970 women.

## Outcome Ascertainment

To monitor health outcomes in the LACE cohort, a health status update questionnaire was mailed to participants semiannually until April 2006 and annually thereafter. The health status update asked women about any events that might have occurred in the preceding 6 mo (or 12 mo on the revised questionnaire), including recurrences, hospitalizations, new primaries, and other cancers. Those women who reported an event were then called on the telephone to obtain details about the reported event. In addition, nonrespondents to the mailed health status update questionnaire were telephoned and asked about any new events. A mortality search was undertaken when nonrespondents could not be reached by telephone and no information had come from other sources regarding those participants' vital status. All reported deaths, including date and cause, were confirmed by death certificate; recurrences were verified by medical chart review. Outcome ascertainment was updated regularly on all participants, including those who dropped out ($n$ = 90) or were lost to active follow-up ($n$ = 15) for whom outcomes were ascertained by regular surveillance of electronic outpatient, cancer registry, and mortality files. The mean follow-up time was 87 mo (SD, 18 mo).

In this analysis, the outcomes of interest were all-cause mortality, breast cancer mortality, and breast cancer recurrence, defined as local, regional, or distant recurrence or metastasis or death from breast cancer if no recurrence was previously reported. A new primary in the contralateral breast was not considered to be a recurrence.

## Assessment of Physical Activity

Physical activity was assessed in the LACE study with a questionnaire based on the Arizona Activity Frequency Questionnaire, which has been validated against doubly labeled water (20). The primary differences between the Arizona Activity Frequency Questionnaire and the LACE physical activity questionnaire are the addition in the latter of activities in the occupational domain and an expansion of the timeframe from 1 mo to 6 mo.

In addition to assessment of job or work-related activities (including volunteer work), the LACE physical activity questionnaire assesses three other domains of activity: nonwork routine activities, recreational activities, and transportation. The routine activities are further subdivided into household chores (6 items), caregiving (5 items), and home maintenance and repairs (7 items). Recreational activities are subdivided into sports, exercise, and dance (22 items), and sedentary recreational activities such as reading or socializing (6 items). Transportation is assessed with four items that ask about motorized or active transport. Respondents were asked to mark each activity they did at least once a month during the previous 6 mo, along with categorical responses indicating frequency and duration of participation. Standard MET values (21) were assigned to each activity and then frequency was multiplied by duration and MET value and summed over all activities (other than the sedentary recreational and transportation activities), providing a summary measure of total activity in MET-h/wk. In addition, a summary score in MET-h/wk was created for moderate to vigorous physical activity by summing the product of frequency, duration, and intensity over only those activities with a MET value of ≥3. Two other summary scores in h/wk were created for time in moderate-intensity activities (3–<6 METs) and time in vigorous-intensity activities (≥6 METs). Finally, a summary score of selected recreational activities, measured in MET-h/wk and termed the Nurses' Health Study activity score, was created to be comparable with the activity measure in the Nurses' Health Study (14) by selecting only those eight specific activities that were assessed in that study (walking or hiking outdoors, jogging or running, bicycling, swimming laps, tennis, calisthenics, aerobics, and squash or racquetball).

## Covariates

The covariates in these analyses were demographic, lifestyle, and medical prognostic factors that, based on the existing literature and *a priori* hypotheses, could potentially confound or modify an association between physical activity and recurrence or mortality. Traditional breast cancer risk factors, such as parity and age at menarche, which were not associated with recurrence or survival in preliminary analyses of the LACE cohort,[3] were not considered for the current analysis. The demographic covariates included age (calculated as the difference between date of enrollment and reported date of birth), race, and education, the last two being self-reported at baseline. Lifestyle factors included smoking status (never, former, current), body mass index (BMI) at enrollment (calculated as weight in kilograms/height in square meters, or $kg/m^2$, from self-reported weight and height), and weight at age 18 (also self-reported at time of enrollment). Medical factors were obtained from electronic databases for the LACE participants who were Kaiser Permanente members and from medical chart review for those who were not, and included tumor size, histology, lymph node involvement and distant metastasis, estrogen and progesterone receptor status, and treatments (type of surgery, radiation and/or chemotherapy, and use of tamoxifen). Tumor stage was classified according to the American Joint Committee on Cancer (3rd edition of manual for staging of cancer). Finally, family history of breast cancer and menopausal status at the time of diagnosis, both self-reported at enrollment, also were considered.

## Statistical Analyses

Differences in means and proportions of each potential covariate between women with each of the three outcomes of interest (recurrence, breast cancer mortality, and all-cause mortality) and women without the specific outcome were compared using *t* tests for continuous variables and $\chi^2$ tests for categorical variables. The level of physical activity in the cohort was described by medians and interquartile ranges to account for the skewed

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distributions, and the physical activity variables were also categorized and described by proportions. ANOVA was used to compare differences in each of the continuous demographic, behavioral, and disease factors across categories of hours per week of moderate-intensity activity. Similarly, $\chi^2$ tests were used to assess differences in each of the categorical factors across levels of moderate-intensity activity.

Separate delayed entry Cox proportional hazards models, with time since diagnosis as the time scale, were used to estimate the risk, expressed as a hazard ratio and 95% confidence interval, of each outcome associated with each activity variable, accounting for varying times of enrollment into the cohort and adjusting for confounders. Follow-up time ended at date of first confirmed recurrence or date of death, depending on the specific analysis. Individuals who did not have a recurrence or who died were censored at date of last contact (either most recent health status update questionnaire or electronic surveillance).

After running age-adjusted models for each activity variable, those disease-related variables that showed bivariate relations with either the independent or dependent variable were added to the model, using a forward stepwise regression to exclude individual variables with $P >$ 0.10. Demographic and behavioral factors were then added using the same approach. Highly collinear variables, such as tamoxifen use and estrogen receptor status, were not entered into the same model, and the decision about which to use in the final model was based on which variable most affected the hazard ratio associated with the physical activity variable.

For all of these models, the physical activity variables were categorized as follows: (*a*) total physical activity and moderate to vigorous physical activity in quartiles based on the distribution in the sample; (*b*) h/wk of moderate physical activity categorized as described above (<1 h/wk, 1–<3 h/wk, 3–<6 h/wk, and ≥6 h/wk); (*c*) h/wk of vigorous physical activity categorized as none, >0–<1, and ≥1; and (*d*) the Nurses' Health Study summary score dichotomized as <9 and ≥9 MET-h/wk.

Effect modification by BMI, estrogen/progesterone receptor status, and menopausal status was examined by stratification. All analyses were conducted in SAS 9.1.3.

## Results

As shown in Table 1, most of the differences at study entry between women who had a recurrence of their breast cancer ($n = 225$) and those who did not were related to the severity of their initial disease and their subsequent treatment. Specifically, those with a recurrence were more likely to have been diagnosed with stage IIb or IIIa tumors (34.8% versus 16.8%; $P < 0.0001$) and to have had chemotherapy and a mastectomy, rather than breast conserving surgery. They were also less likely to have negative nodes (43.7% versus 66.9%, $P <$ 0.0001) or estrogen receptor–positive/progesterone receptor–positive status (59.8% versus 69.4%, $P = 0.01$). The only demographic, health status, or behavioral factor that differed between the two groups was reported weight at age 18 years, which was statistically significantly higher in women who had a recurrence (123.7 lbs; SD, 17.6 versus 120.8 lbs; SD, 17.0; $P = 0.02$). Similarly, women who died from breast cancer ($n = 102$) had more severe disease, as indicated by stage, treatment, nodal status, and estrogen and/or progesterone receptor status, although this latter difference was only of borderline significance. The women who died from breast cancer also reported a higher weight at age 18 and were slightly older than the rest of the cohort (62.5 years; SD, 10.7 versus 60.4 years; SD, 10.8; $P = 0.06$). In contrast, the women who died of any cause ($n = 187$), not only had more advanced breast cancer than those who survived, but also differed in other ways; they were older (65.3 years; SD, 10.5 versus 60.0 years; SD, 10.7; $P < 0.0001$), heavier at enrollment (mean self-reported BMI = 28.6 kg/m$^2$; SD, 6.5 versus 27.3 kg/m$^2$; SD, 5.7; $P =$

0.01) as well as at age 18, more likely to be postmenopausal (77.5% versus 63.7%; $P$ = 0.0004) and to be past or current smokers (57.7% versus 45.1%; $P$ = 0.0003), and less likely to have a college degree (23.5% versus 37.4%, $P$ = 0.0003).

In general, the level of reported physical activity was relatively high (Table 2); 49% of the cohort reported participating in moderate-intensity activity for ≥3 hours/week, 44% reported participating in at least some vigorous activity, and 42% reported at least 9 MET-hours/week of selected recreational activities. As Table 3 shows, women who reported more time in moderate intensity activity tended to be younger, better educated, and leaner, and were less likely to be postmenopausal. They were also less likely to have had =3 positive nodes but slightly more likely to have had chemotherapy. The associations between the other physical activity variables and demographic and disease characteristics were similar (data not shown).

Table 4 presents age-adjusted and fully adjusted risks of breast cancer recurrence and mortality and all-cause mortality associated with each of the physical activity variables. Although the hazard ratio for recurrence was consistently reduced for women who did some activity, relative to those at the lowest end of the activity spectrum, there was little evidence for a dose-response relation, and the only trend that was significant was for time spent in moderate-intensity physical activity. A similar pattern was observed for risk of breast cancer mortality. However, the relation between physical activity and all-cause mortality did not follow the same pattern as the other two outcomes, and risk declined significantly as activity increased for all the physical activity variables except hours per week of vigorous physical activity. Multivariable models that adjusted for disease prognostic factors and other potential confounders attenuated all of the risk ratios associated with physical activity, even for all-cause mortality, in which the only protective associations that remained significant or marginally significant were with MET-hours per week of moderate to vigorous physical activity ($P$ for trend = 0.06) and hours per week of moderate physical activity ($P$ for trend = 0.04).

Subgroup analyses suggested that the trend for reduced risk of all-cause mortality associated with time spent in moderate-intensity physical activity was statistically significant only in postmenopausal women and not in premenopausal women, among whom 17 of 21 deaths were due to breast cancer (data not shown). The reduced risk of all-cause mortality associated with time spent in moderate-intensity physical activity also varied by BMI at time of enrollment and by estrogen/progesterone receptor status (Table 5). Risk was significantly reduced, in a dose-response relation, in normal-weight women (BMI <25) but not in either overweight or obese women. Also, risk was significantly reduced among women with estrogen receptor–positive/progesterone receptor–positive tumors but not in those who are estrogen receptor negative and/or progesterone receptor negative. Differential effects of physical activity by either menopausal status, BMI, or receptor status were not observed for either breast cancer recurrence or breast cancer mortality (data not shown).

To examine the potential effect of preexisting recurrence on these findings, all models described above were repeated excluding the 33 women who had recurrences within 1 year of enrollment. The results from these sensitivity analyses were essentially unchanged (data not shown).

## Discussion

In this cohort of breast cancer survivors, there was some evidence that higher levels of physical activity, expressed either in terms of MET-hours per week of all activities of at least moderate intensity, or simply as hours per week of only moderate (and not vigorous)

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activity, were associated with reduced risk of recurrence and breast cancer mortality. This suggestion disappeared, however, once the risk estimates were adjusted for prognostic factors and other confounding variables. In contrast, a generally consistent and statistically significant protective association was observed between physical activity and all-cause mortality, even in multivariable analyses.

The finding of a protective association between physical activity and all-cause mortality is consistent with other cohort studies of breast cancer survivors (14, 16). However, the absence of any association with breast cancer mortality, although consistent with at least one other published report (22), does not agree with the findings reported by Holmes et al. in the Nurses' Health Study (14) or Holick et al. in the Collaborative Women's Longevity Study (15). Both studies used the same measure of physical activity, but even when that variable was reproduced in the current study, the findings were not replicated. One reason for this discrepancy may be a difference in both overall sample size and the number of reported outcomes; although the Nurses' Health Study had a sample size that was about 33% larger than LACE (2,987 versus 1,970), the number of breast cancer deaths was almost three times greater (280 versus 102). This may reflect, in part, the slightly longer follow-up period in the Nurses' Health Study (96 months versus 87 months), but may also suggest that the LACE cohort is not directly comparable with either the Nurses' Health Study or the Collaborative Women's Longevity Study cohort. In the LACE cohort, the mean BMI at study entry among the most active women was 26.2 kg/m$^2$, which was almost identical to the mean among the least active in the Nurses' Health Study (26.4 kg/m$^2$), indicating that the women in the Nurses' Health Study cohort were considerably leaner than those in the LACE cohort. In the Collaborative Women's Longevity Study, the cohort was also leaner, better educated, and almost entirely white. Because heavier women may overestimate their physical activity (23), the LACE findings may be more subject to misclassification, which would tend to attenuate any true association that might exist.

Nevertheless, the risk estimates for recurrence and breast cancer mortality associated with physical activity reported here are generally in the expected protective direction, although they are not statistically significant, and, as reported by the Nurses' Health Study, were more pronounced in women with estrogen receptor–positive/progesterone receptor–positive tumors. To that extent, the current findings are generally in agreement with the Nurses' Health Study and the Collaborative Women's Longevity Study findings and are weakly supportive of a protective association with physical activity.

One notable anomaly in the findings reported here is that the risk estimates associated with vigorous activity showed little or no evidence of a protective association for any of the outcomes, including all-cause mortality, in contrast to those associated with moderate activity. This was also observed in the Collaborative Women's Longevity Study (15). In part, this anomaly may be attributable to measurement error from overreporting, given that 44% of LACE women reported at least some weekly participation in activity of ≥6 METs. Considering the age of the cohort, and the national prevalence of vigorous activity in women ages 45 to 64 years (28%; ref. 24), the proportion in LACE reporting vigorous physical activity is unexpected. On the other hand, it is also possible that the absence of association between vigorous physical activity and any of the outcomes of interest was due to the fact that some women with more severe or aggressive disease engaged in vigorous physical activity as a means to cope with disease and treatment effects. A substantial body of literature indicates that exercise training in breast cancer survivors, both during and after treatment, enhances quality of life, reduces symptoms, and improves cardiorespiratory fitness and physical function (25–29), which may influence women to adopt exercise as a behavioral strategy for managing their disease.

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A number of biological mechanisms, such as decreased lifetime exposure to cyclical estrogen and progesterone, decreased body fat and long-term maintenance of energy balance, and an improved metabolic profile (i.e. lower fasting glucose, heightened insulin sensitivity, lower levels of unbound insulin-like growth factors, and improved immune function; ref. 3, 4, 30), have been hypothesized to account for the protective relation between physical activity and breast cancer incidence. These mechanisms could also act, after diagnosis, to decrease the risk of recurrence and improve survival. Several intervention studies have shown that exercise training in breast cancer survivors has resulted in improvements in the cardiovascular disease risk profile (lower C-reactive protein and blood pressure; ref. 31), decreases in body fat (32), changes in insulin-like growth factors (33), and better immune function (34). Although such physiologic changes might be expected to translate into decreased risk of recurrence and increased likelihood of survival, it is not clear what level of physical activity is required to produce these training effects. It is possible that the required level generally exceeds that usually observed in the population of breast cancer survivors at large.

In evaluating the study findings, some limitations should be considered. Most important is the reliance on self-report of physical activity, which always introduces some degree of recall error (23, 35–37). As noted above, there may have been overreporting, particularly of vigorous-intensity physical activity. However, the physical activity variables in LACE show the expected relations with correlates of activity, such as age, BMI, and education, suggesting that these variables rank individuals reasonably correctly, even if the point estimates are not precise. Secondly, no measures of physical activity prior to diagnosis were available for the LACE cohort. Given the potential impact of physical activity on lifetime hormonal exposure, it may be that prediagnosis physical activity, or even lifetime physical activity, combined with postdiagnosis physical activity, is most influential in determining recurrence and survival. However, a study by Enger and Bernstein (13) of premenopausal women with breast cancer found no association between lifetime exercise and survival and only a weak, statistically nonsignificant association for recent, prediagnosis activity. In addition, the findings in the Collaborative Women's Longevity Study were unchanged with adjustment for either early-life exercise or prediagnosis activity, suggesting little confounding of postdiagnosis physical activity by earlier physical activity (15). Finally, the relatively small number of recurrences and deaths may suggest some degree of selection bias in terms of a healthier, more robust cohort that might contribute to the null findings. However, a comparison of the enrollees and nonenrollees revealed no significant differences in stage of disease, number of positive nodes, or tumor size, and also showed that older women were more likely to enroll than younger women (18). Perhaps more importantly, the relatively small number or outcomes may have limited statistical power; the consistently reduced, but nonsignificant, risk estimates for higher levels of physical activity suggests this possibility.

This study also has strengths worth considering. First, the sample represents a broad spectrum of the population (about 25% have a high school education or less and about 20% are racial/ethnic minorities). Secondly, physical activity was assessed in several domains, allowing for a more comprehensive measure that includes more of the activities in which women actually engage. Also physical activity was assessed following treatment, which allows for examination of the effect of activity during the survival period when the behavior was less likely to be impacted by the consequences of disease.

In conclusion, despite the lack of statistically significant protective associations between physical activity and breast cancer recurrence and mortality in this study, the public health implications of the findings are clear. For breast cancer survivors, engaging in regular physical activity is beneficial in terms of total mortality, just as it is in the population at large. Although physical activity may or may not reduce the risk of recurrence, it does not increase the risk and provides other important benefits in terms of improved quality of life, physical function, and physical fitness.

## Acknowledgments

We thank all LACE Study staff and participants.

Grant support: National Cancer Institute (R01 CA80027) and by the Utah Cancer Registry (N01 PC67000) with additional support from the State of Utah Department of health.

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## Table 1

Characteristics of LACE cohort at study entry by outcome

| | Recurrence* | | | Deceased, breast cancer | | | Deceased, all causes | | |
|---|---|---|---|---|---|---|---|---|---|
| | No (*n* = 1,745) | Yes (*n* = 225) | *P*† | No (*n* = 1,868) | Yes (*n* = 102) | *P*† | No (*n* = 1,783) | Yes (*n* = 187) | *P*† |
| Person-years of follow-up | 601 | 9,788 | - | 345 | 10,478 | - | 697 | 10,125 | - |
| Age at enrollment, mean y (SD) | 60.6 (10.8) | 60.4 (10.9) | 0.80 | 60.4 (10.8) | 62.5 (10.7) | 0.06 | 60.0 (10.7) | 65.3 (10.5) | <0.0001 |
| Race, *n* (%) | | | 0.93 | | | 0.57 | | | 0.77 |
| White | 1,421 (81.5) | 184 (81.8) | | 1,524 (81.7) | 81 (79.4) | | 1,451 (81.5) | 154 (82.4) | |
| Other | 322 (18.5) | 41 (18.2) | | 342 (18.3) | 21(20.6) | | 330 (18.5) | 33 (17.6) | |
| Education, *n* (%) | | | 0.87 | | | 0.27 | | | 0.0003 |
| High school graduate or less | 464 (26.7) | 63 (28.0) | | 494 (26.5) | 33 (32.4) | | 459 (25.8) | 68 (36.4) | |
| Some college | 646 (37.1) | 84 (37.3) | | 691 (37.1) | 39 (38.2) | | 655 (36.8) | 75 (40.1) | |
| College graduate or more | 631 (36.2) | 78 (34.7) | | 679 (36.4) | 30 (29.4) | | 665 (37.4) | 44 (23.5) | |
| Smoking status, *n* (%) | | | 0.27 | | | 0.38 | | | 0.0003 |
| Never | 940 (54.2) | 112 (49.8) | | 1,003 (54.0) | 49 (48.0) | | 973 (54.9) | 79 (42.3) | |
| Past | 676 (39.0) | 92 (40.9) | | 725 (39.0) | 43 (42.2) | | 684 (38.6) | 84 (44.9) | |
| Current | 119 (6.8) | 21 (9.3) | | 130 (7.0) | 10 (9.8) | | 116 (6.5) | 24 (12.8) | |
| BMI at enrollment, mean $kg/m^2$ (SD) | 27.4 (5.8) | 27.9 (6.1) | 0.31 | 27.4 (5.8) | 28.3 (6.1) | 0.14 | 27.3 (5.7) | 28.6 (6.5) | 0.01 |
| Weight at 18 y, mean lbs (SD) | 120.8 (17.0) | 123.7 (17.6) | 0.02 | 120.9 (16.9) | 125.6 (19.2) | 0.02 | 120.8 (17.0) | 123.9 (17.9) | 0.03 |
| Menopausal status, *n* (%) | | | 0.76 | | | 0.51 | | | 0.0004 |
| Postmenopausal | 1,139 (65.3) | 142 (63.1) | | 1,211 (64.8) | 70 (68.6) | | 1,136 (63.7) | 145 (77.5) | |
| Premenopausal | 370 (21.2) | 49 (21.8) | | 402 (21.5) | 17 (16.7) | | 398 (22.3) | 21 (11.2) | |
| Undetermined | 236 (13.5) | 34 (15.1) | | 255 (13.7) | 15 (14.7) | | 249 (14.0) | 21 (11.2) | |
| Family history of breast cancer, *n* (%) | | | 0.98 | | | 0.96 | | | 0.69 |
| No | 1,388 (79.6) | 179 (79.6) | | 1,486 (79.6) | 81 (79.4) | | 1,416 (79.5) | 151 (80.7) | |
| Yes | 355 (20.4) | 46 (20.4) | | 380 (20.4) | 21 (20.6) | | 365 (20.5) | 36 (19.3) | |
| Stage, *n* (%) | | | <0.0001 | | | <0.0001 | | | <0.0001 |
| I | 867 (49.8) | 73 (32.6) | | 915 (49.1) | 25 (24.5) | | 878 (49.3) | 62 (33.3) | |
| IIa | 582 (33.4) | 73 (32.6) | | 623 (33.4) | 32 (31.4) | | 593 (33.3) | 62 (33.3) | |
| IIb | 256 (14.7) | 58 (25.9) | | 282 (15.1) | 32 (31.4) | | 266 (14.9) | 48 (25.8) | |
| IIIa | 37 (2.1) | 20 (8.9) | | 44 (2.4) | 13 (12.7) | | 43 (2.4) | 14 (7.5) | |

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| | Recurrence* | | | Deceased, breast cancer | | | Deceased, all causes | | |
|---|---|---|---|---|---|---|---|---|---|
| | No ($n$ = 1,745) | Yes ($n$ = 225) | $P$† | No ($n$ = 1,868) | Yes ($n$ = 102) | $P$† | No ($n$ = 1,783) | Yes ($n$ = 187) | $P$† |
| Type of surgery, $n$ (%) | | | 0.001 | | | 0.02 | | | 0.01 |
| Conserving | 902 (51.7) | 91 (40.4) | | 953 (51.0) | 40 (39.2) | | 915 (51.3) | 78 (41.7) | |
| Mastectomy | 842 (48.3) | 134 (59.6) | | 914 (49.0) | 62 (60.8) | | 867 (48.7) | 109 (58.3) | |
| Chemotherapy, $n$ (%) | | | <0.0001 | | | 0.01 | | | 0.62 |
| No | 786 (45.4) | 70 (31.5) | | 825 (44.5) | 31 (31.3) | | 773 (43.7) | 83 (45.6) | |
| Yes | 944 (54.6) | 152 (68.5) | | 1,028 (55.5) | 68 (68.7) | | 997 (56.3) | 99 (54.4) | |
| Radiation therapy, $n$ (%) | | | 0.33 | | | 0.06 | | | 0.38 |
| No | 639 (37.5) | 75 (34.1) | | 686 (37.6) | 28 (28.3) | | 653 (37.4) | 61 (34.1) | |
| Yes | 1,066 (62.5) | 145 (65.9) | | 1,140 (62.4) | 71 (71.7) | | 1,093 (62.6) | 118 (65.9) | |
| Number of positive nodes, $n$ (%) | | | <0.0001 | | | <0.0001 | | | <0.0001 |
| Node negative | 1,097 (66.9) | 90 (43.7) | | 1,154 (66.0) | 33 (34.0) | | 1,105 (66.2) | 82 (46.1) | |
| 1–3 | 409 (24.9) | 60 (29.1) | | 435 (24.9) | 34 (35.1) | | 418 (25.1) | 51 (28.6) | |
| ≥3 | 134 (8.2) | 56 (27.2) | | 160 (9.1) | 30 (30.9) | | 145 (8.7) | 45 (25.3) | |
| Tamoxifen use, $n$ (%) | | | 0.31 | | | 0.79 | | | 0.09 |
| No | 389 (22.3) | 57 (25.3) | | 424 (22.7) | 22 (21.6) | | 413 (23.2) | 33 (17.6) | |
| Yes | 1,356 (77.7) | 168 (74.7) | | 1,444 (77.3) | 80 (78.4) | | 1,370 (76.8) | 154 (82.4) | |
| ER/PR receptor status, $n$ (%) | | | 0.01 | | | 0.06 | | | 0.03 |
| ER+, PR+ | 1,196 (69.4) | 131 (59.8) | | 1,268 (68.8) | 59 (59.6) | | 1,212 (68.9) | 115 (62.8) | |
| ER+, PR− | 239 (13.9) | 36 (16.4) | | 256 (13.9) | 19 (19.2) | | 238 (13.5) | 37 (20.2) | |
| ER−, PR+ | 27 (1.6) | 8 (3.7) | | 31 (1.7) | 4 (4.0) | | 29 (1.7) | 6 (3.3) | |
| ER−, PR− | 260 (15.1) | 44 (20.1) | | 288 (15.6) | 17 (17.2) | | 279 (15.9) | 25 (13.7) | |
| Time from diagnosis to enrollment, mean y (SD) | 1.9 (0.6) | 1.9 (0.6) | 0.54 | 1.9 (0.6) | 1.9 (0.6) | 0.87 | 1.9 (0.6) | 1.9 (0.5) | 0.50 |

Abbreviations: ER+, estrogen receptor positive; ER−, estrogen receptor negative; PR+, progesterone receptor positive; PR−, progesterone receptor negative.

*Recurrence includes local, regional, or distant recurrence or metastasis or death from breast cancer if no recurrence was previously reported.

†$P$ value for $t$ test for difference in means, or $\chi^2$ test for difference in proportions between women with and without the event.

**Table 2**

Level of physical activity in LACE cohort at study entry

| | |
|---|---|
| Total activity, median MET-h/wk (I-Q range) | 44.3 (29.3–62.3) |
| Moderate-vigorous activity, median MET-h/wk (I-Q range) | 14.8 (5.3–27.2) |
| Moderate activity, median h/wk(I-Q range) | 2.9 (1.0–5.6) |
| Categorized in h/wk, *n* (%) | |
| <1 | 490 (25%) |
| 1–<3 | 502 (26%) |
| 3–<6 | 524 (27%) |
| ≥6 | 434 (22%) |
| Vigorous activity, median h/wk (I-Q range) | 0.0 (0–1.1) |
| Categorized in h/wk, *n* (%) | |
| 0 | 1,102 (56%) |
| >0–<1 | 356 (18%) |
| ≥1 | 505 (26%) |
| Selected activities, median MET-h/wk (I-Q range) | 5.9 (0–16.5) |
| Categorized in h/wk, *n* (%) | |
| <9 | 1,099 (58%) |
| ≥9 | 804 (42%) |

**Table 3**

Characteristics of LACE cohort by hours/week of moderate intensity physical activity

| | Hours per week of moderate activity | | | | P* |
|---|---|---|---|---|---|
| | **<1 h (*n* = 490)** | **1–<3 h (*n* = 502)** | **3–<6 h (*n* = 523)** | **≥6 h (*n* = 433)** | |
| Age at enrollment, mean y (SD) | 62.8 (11.1) | 60.0 (11.2) | 59.9 (10.3) | 59.6 (10.2) | <0.0001 |
| Race, *n* (%) | | | | | 0.15 |
| White | 383 (78.2) | 409 (81.5) | 432 (82.6) | 362 (83.6) | |
| Other | 107 (21.8) | 93 (18.5) | 91 (17.4) | 71 (16.4) | |
| Education, *n* (%) | | | | | 0.0001 |
| High school graduate or less | 167 (34.1) | 125 (24.9) | 116 (22.2) | 116 (26.9) | |
| Some college | 178 (36.3) | 201 (40.0) | 198 (37.9) | 143 (33.2) | |
| College graduate or more | 145 (29.6) | 176 (35.1) | 209 (40.0) | 172 (39.9) | |
| Smoking status, *n* (%) | | | | | 0.40 |
| Never | 263 (53.8) | 279 (55.8) | 269 (51.6) | 234 (54.3) | |
| Past | 184 (37.6) | 187 (37.4) | 222 (42.6) | 165 (38.3) | |
| Current | 42 (8.6) | 34 (6.8) | 30 (5.8) | 32 (7.4) | |
| BMI at enrollment, mean $kg/m^2$ (SD) | 28.9 (6.3) | 27.9 (5.8) | 26.9 (5.6) | 26.2 (5.1) | <0.0001 |
| Weight at 18 y, mean lbs (SD) | 120.5 (17.6) | 120.4 (16.2) | 122.5 (17.3) | 120.6 (16.9) | 0.16 |
| Menopausal status, *n* (%) | | | | | 0.03 |
| Postmenopausal | 340 (69.4) | 315 (62.8) | 333 (63.5) | 286 (65.9) | |
| Premenopausal | 95 (19.4) | 117 (23.3) | 100 (19.1) | 97 (22.4) | |
| Undetermined | 55 (11.2) | 70 (13.9) | 91 (17.4) | 51 (11.7) | |
| Family history of breast cancer, *n* (%) | | | | | 0.74 |
| No | 389 (79.4) | 408 (81.3) | 411 (78.6) | 343 (79.2) | |
| Yes | 101 (20.6) | 94 (18.7) | 112 (21.4) | 90 (20.8) | |
| Stage, *n* (%) | | | | | 0.21 |
| I | 218 (44.7) | 233 (46.5) | 257 (49.1) | 219 (50.6) | |
| IIa | 163 (33.4) | 180 (35.9) | 160 (30.5) | 147 (34.0) | |
| IIb | 94 (19.3) | 72 (14.4) | 90 (17.2) | 56 (12.9) | |
| IIIa | 13 (2.7) | 16 (3.2) | 17 (3.2) | 11 (2.5) | |
| Type of surgery, *n* (%) | | | | | 0.60 |

| | Hours per week of moderate activity | | | | $P^*$ |
|---|---|---|---|---|---|
| | <1 h (*n* = 490) | 1–<3 h (*n* = 502) | 3–<6 h (*n* = 523) | ≥6 h (*n* = 433) | |
| Conserving | 244 (49.8) | 265 (52.8) | 255 (48.7) | 218 (50.3) | |
| Mastectomy | 246 (50.2) | 237 (47.2) | 269 (51.3) | 215 (49.7) | |
| Chemotherapy, *n* (%) | | | | | 0.03 |
| No | 232 (48.2) | 195 (39.0) | 230 (44.3) | 188 (43.5) | |
| Yes | 249 (51.8) | 305 (61.0) | 289 (55.7) | 244 (56.5) | |
| Radiation therapy, *n* (%) | | | | | 0.83 |
| No | 179 (38.2) | 176 (35.6) | 197 (37.9) | 155 (36.8) | |
| Yes | 290 (61.8) | 319 (64.4) | 323 (62.1) | 266 (63.2) | |
| Number of positive nodes, *n* (%) | | | | | 0.06 |
| Node negative | 282 (60.6) | 291 (62.1) | 319 (65.8) | 283 (68.9) | |
| 1–3 | 125 (26.9) | 121 (25.8) | 121 (24.9) | 99 (24.1) | |
| ≥3 | 58 (12.5) | 57 (12.1) | 45 (9.3) | 29 (7.1) | |
| Tamoxifen use, *n* (%) | | | | | .69 |
| No | 116 (23.7) | 121 (24.1) | 113 (21.6) | 94 (21.7) | |
| Yes | 374 (76.3) | 381 (75.9) | 411 (78.4) | 340 (78.3) | |
| ER/PR receptor status, *n* (%) | | | | | 0.33 |
| ER+, PR+ | 330 (68.6) | 319 (64.4) | 366 (70.8) | 296 (69.0) | |
| ER+, PR− | 62 (12.9) | 73 (14.8) | 71 (13.7) | 67 (15.6) | |
| ER−, PR+ | 6 (1.2) | 12 (2.4) | 9 (1.7) | 7 (1.6) | |
| ER−, PR− | 83 (17.3) | 91 (18.4) | 71 (13.7) | 59 (13.8) | |
| Time from diagnosis to enrollment, mean y (SD) | 1.9 (0.5) | 1.9 (0.6) | 1.9 (0.6) | 1.9 (0.6) | 0.91 |
| Follow-up time, mean y (SD) | | | | | |
| To recurrence | 7.0 (1.6) | 7.2 (1.6) | 7.2 (1.5) | 7.2 (1.5) | 0.08 |
| To death | 7.2 (1.3) | 7.4 (1.3) | 7.4 (1.2) | 7.4 (1.3) | 0.08 |

* ANOVA to test for differences in means of continuous variables; chi-square tests to evaluate differences in proportions for categorical variables.

**Table 4**

Risk of breast cancer recurrence, breast cancer mortality and all-cause mortality associated with physical activity

| | Recurrence ($n$ = 225) | | Breast cancer mortality ($n$ = 102) | | All-cause mortality ($n$ = 187) | |
|---|---|---|---|---|---|---|
| | Model I* | Model II† | Model I* | Model II‡ | Model I* | Model II§ |
| | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| Total activity, MET-h/wk | | | | | | |
| Q1 (<29) | Ref | Ref | Ref | Ref | Ref | Ref |
| Q2 (29–<44) | 0.65 (0.44–0.97) | 0.76 (0.51–1.13) | 0.83 (0.49–1.40) | 1.01 (0.57–1.78) | 0.70 (0.47–1.04) | 0.89 (0.59–1.33) |
| Q3 (44–<62) | 0.82 (0.57–1.19) | 0.87 (0.59–1.29) | 0.71 (0.41–1.24) | 0.70 (0.38–1.29) | 0.67 (0.45–1.00) | 0.82 (0.54–1.25) |
| Q4 (≥62) | 0.79 (0.54–1.15) | 0.91 (0.61–1.36) | 0.68 (0.39–1.18) | 0.87 (0.48–1.59) | 0.58 (0.38–0.88) | 0.76 (0.48–1.19) |
| *P for trend* | 0.40 | 0.78 | 0.14 | 0.41 | 0.01 | 0.20 |
| Moderate-vigorous activity, MET-h/wk | | | | | | |
| Q1 (<5.3) | Ref | Ref | Ref | Ref | Ref | Ref |
| Q2 (5.3–<15) | 0.67 (0.46–0.97) | 0.73 (0.49–1.09) | 0.68 (0.41–1.15) | 0.77 (0.44–1.34) | 0.63 (0.43–0.93) | 0.71 (0.48–1.07) |
| Q3 (15–<27) | 0.62 (0.42–0.91) | 0.75 (0.50–1.12) | 0.47 (0.26–0.85) | 0.47 (0.24–0.91) | 0.49 (0.32–0.74) | 0.58 (0.37–0.90) |
| Q4 (≥27) | 0.84 (0.59–1.20) | 1.00 (0.68–1.46) | 0.68 (0.41–1.15) | 0.90 (0.51–1.58) | 0.56 (0.38–0.83) | 0.74 (0.49–1.13) |
| *P for trend* | 0.31 | 0.95 | 0.07 | 0.38 | 0.001 | 0.06 |
| H/wk of moderate activity | | | | | | |
| <1 | Ref | Ref | Ref | Ref | Ref | Ref |
| 1–<3 | 0.76 (0.53–1.09) | 0.81 (0.55–1.18) | 0.51 (0.29–0.89) | 0.65 (0.36–1.16) | 0.59 (0.40–0.87) | 0.71 (0.48–1.06) |
| 3–<6 | 0.80 (0.56–1.13) | 0.86 (0.60–1.25) | 0.69 (0.42–1.13) | 0.69 (0.40–1.19) | 0.57 (0.39–0.84) | 0.66 (0.44–1.00) |
| ≥6 | 0.66 (0.44–0.97) | 0.81 (0.54–1.22) | 0.56 (0.32–0.98) | 0.73 (0.40–1.33) | 0.51 (0.34–0.79) | 0.66 (0.42–1.03) |
| *P for trend* | 0.05 | 0.36 | 0.07 | 0.26 | 0.001 | 0.04 |
| Hours/wk of vigorous activity | | | | | | |
| 0 | Ref | Ref | Ref | Ref | Ref | Ref |
| >0–<1 | 0.88 (0.61–1.28) | 0.91 (0.62–1.36) | 0.72 (0.40–1.28) | 0.79 (0.42–1.48) | 0.74 (0.48–1.15) | 0.90 (0.57–1.41) |
| ≥1 | 1.06 (0.78–1.44) | 1.12 (0.81–1.56) | 0.85 (0.53–1.36) | 1.10 (0.68–1.80) | 0.87 (0.61–1.23) | 1.02 (0.70–1.47) |
| *P for trend* | 0.80 | 0.58 | 0.40 | 0.82 | 0.33 | 1.0 |
| Selected activities, MET-h/wk | | | | | | |
| <9 | Ref | Ref | Ref | Ref | Ref | Ref |
| ≥9 | 1.00 (0.76–1.31) | 1.16 (0.87–1.55) | 0.91 (0.61–1.36) | 1.19 (0.78–1.84) | 0.78 (0.57–1.06) | 0.98 (0.71–1.35) |

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HR, hazard ratio; 95% CI, 95% confidence interval.

* Adjusted for age.

† Adjusted for age, number of positive nodes, stage and weight at 18 y.

‡ Adjusted for age, number of positive nodes, stage, weight at 18 y, type of treatment (chemotherapy/radiation) and type of surgery (mastectomy or conserving).

§ Adjusted for age, number of positive nodes, stage, weight at 18 y, education level and smoking status.

## Table 5

Multivariable adjusted risk of all-cause mortality associated with moderate intensity physical activity stratified by baseline BMI and ER/PR receptor status

| | **BMI at enrollment, kg/m$^2$** | | |
|---|---|---|---|
| | **<25 (*n* = 749)** | **25–29.9 (*n* = 656)** | **>30 (*n* = 518)** |
| | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |
| H/wk of moderate activity | | | |
| <1 | Ref | Ref | Ref |
| 1–<3 | 0.52 (0.25–1.10) | 0.73 (0.37–1.43) | 0.84 (0.42–1.70) |
| 3–<6 | 0.42 (0.20–0.90) | 0.74 (0.38–1.45) | 0.89 (0.42–1.85) |
| >6 | 0.38 (0.17–0.85) | 0.95 (0.47–1.94) | 0.90 (0.38–2.16) |
| *P for trend* | 0.01 | 0.78 | 0.76 |
| | ER/PR receptor status | | |
| | ER and/or PR negative (*n* = 614) | | ER/PR positive (*n* = 1,327) |
| | HR (95% CI) | | HR (95% CI) |
| H/wk of moderate activity | | | |
| <1 | Ref | | Ref |
| 1–<3 | 0.80 (0.41–1.54) | | 0.64 (0.38–1.06) |
| 3–<6 | 1.06 (0.56–2.00) | | 0.46 (0.26–0.79) |
| >6 | 0.75 (0.36–1.59) | | 0.59 (0.34–1.04) |
| *P for trend* | 0.69 | | 0.01 |

NOTE: Adjusted for age at enrollment into cohort, number of positive nodes, stage, weight at 18 y, education level and smoking status.