Published in final edited form as:

Breast Cancer Res Treat. 2010 September ; 123(2): 531–542. doi:10.1007/s10549-010-0774-6.

Past recreational physical activity, body size, and all-cause mortality following breast cancer diagnosis: results from the Breast Cancer Family Registry

Theresa H. M. Keegan^{1,2}, Roger L. Milne^{3,4}, Irene L. Andrulis^{5,6}, Ellen T. Chang^{1,2}, Meera Sangaramoorthy¹, Kelly-Anne Phillips^{7,8}, Graham G. Giles⁹, Pamela J. Goodwin^{5,10}, Carmel Apicella⁴, John L. Hopper⁴, Alice S. Whittemore², and Esther M. John^{1,2}

¹Northern California Cancer Center, Fremont, California, USA

²Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA

³Genetic & Molecular Epidemiology Group, Human Cancer Genetics Program, Spanish National Cancer Center (CNIO), Madrid, Spain

⁴Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, School of Population Health, The University of Melbourne, Victoria, Australia

⁵Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

⁶Ontario Cancer Genetics Network, Cancer Care Ontario, Toronto, Ontario, Canada

⁷Division of Haematology and Medical Oncology, Peter MacCallum Cancer Centre, Victoria, Australia

⁸Department of Medicine, St. Vincent's Hospital, The University of Melbourne, Victoria, Australia

⁹Cancer Epidemiology Centre, The Cancer Council Victoria, Carlton, Victoria, Australia

¹⁰Departments of Medicine and Public Health Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

Abstract

Few studies have considered the joint association of body mass index (BMI) and physical activity, two modifiable factors, with all-cause mortality after breast cancer diagnosis. Women diagnosed with invasive breast cancer (n=4,153) between 1991 and 2000 were enrolled in the Breast Cancer Family Registry through population-based sampling in Northern California, USA; Ontario, Canada; and Melbourne and Sydney, Australia. During a median follow-up of 7.8 years, 725 deaths occurred. Baseline questionnaires assessed moderate and vigorous recreational physical activity and BMI prior to diagnosis. Associations with all-cause mortality were assessed using Cox proportional hazards regression, adjusting for established prognostic factors. Compared with no physical activity, any recreational activity during the three years prior to diagnosis was associated with a 34% lower risk of death (hazard ratio (HR) = 0.66, 95% confidence interval (CI): 0.51-0.85) for women with estrogen receptor (ER)-positive tumors, but not those with ER-negative tumors; this association did not appear to differ by race/ethnicity or BMI. Lifetime physical activity was not associated with all-cause mortality. BMI was positively associated with

all-cause mortality for women diagnosed at age ≥ 50 years with ER-positive tumors (compared with normal-weight women, HR for overweight = 1.39, 95% CI: 0.90-2.15; HR for obese = 1.77, 95% CI: 1.11-2.82). BMI associations did not appear to differ by race/ethnicity. Our findings suggest that physical activity and BMI exert independent effects on overall mortality after breast cancer.

Keywords

breast cancer; physical activity; body mass index; obesity; mortality

Introduction

Worldwide, breast cancer is the most common cancer and the leading cause of cancer death for women [1]. Breast cancer survivors are at risk of recurrence, second cancers, and premature death [2-4]. Therefore, it is critical to identify modifiable factors that can reduce the risk of these conditions and improve prognosis. The association between body size and survival after breast cancer diagnosis has been examined extensively, with most studies reporting that higher body mass index (BMI) was associated with worse survival [5-9]. Few studies, however, have considered the joint associations of body size and physical activity on survival after breast cancer. Thus, it remains unclear whether the apparent prognostic association with BMI is confounded by physical activity or some other related factor.

Increased physical activity has been associated with reduced mortality after breast cancer diagnosis [10-16], particularly in women with hormone receptor positive tumors [10,13-15]. The epidemiologic evidence, however, is not consistent [17-19], possibly due to methodologic differences between studies, such as inclusion of select study populations [10,13,16], the timing of the physical activity assessment relative to diagnosis [16], low response rates to post-diagnostic physical activity assessments [12], select ages of the women studied [11,18], or small sample sizes [17-19]. Most of the studies conducted to date did not include non-white racial/ethnic groups [10,12-14,16,18], and not all studies examined whether associations varied by breast cancer hormone receptor status [12,18].

The present study examined the associations between lifetime and recent recreational physical activity and recent BMI with all-cause mortality, stratified by patient characteristics (i.e., age at diagnosis, family history of breast cancer, race/ethnicity) and tumor hormone receptor status in an international, population-based study of breast cancer.

Materials and Methods

Subjects

This analysis was based on data from three family registries collaborating in the Breast Cancer Family Registry (Breast CFR), an international consortium established in 1995 and funded by the US National Cancer Institute [20]. Female patients newly diagnosed with invasive breast cancer were enrolled from the San Francisco Bay Area, California, USA (1995-2000), Ontario, Canada (1996-1998), and Melbourne and Sydney, Australia (1991-1998). Cases were ascertained through the regional population-based cancer registries, using specific eligibility and sampling criteria that have been described previously [21]. Briefly, in Northern California and Ontario, a two-stage sampling procedure was used to oversample cases with characteristics thought to be indicative of increased genetic susceptibility. A subset of cases not meeting the high-risk criteria was randomly sampled. The Northern California registry also oversampled cases from racial/ethnic minority populations. In Melbourne and Sydney all incident breast cancer cases diagnosed at age <40

years were eligible for enrollment in the Breast CFR, and those aged 40-59 years were randomly sampled at age- and state-specific rates. Approval of the study protocol was obtained from relevant institutional review boards and written informed consent was received from all study participants.

In Northern California, 2,008 cases <65 years of age were invited to enroll in the Breast CFR; of these, 37 were deceased and 1,569 (78%) completed the in-person interview on epidemiologic risk factors. In Ontario, 2,536 cases ≤69 years of age were selected; of these, 25 were deceased and 1,835 (72%) completed a mailed risk factor questionnaire. In Melbourne and Sydney, 1,780 cases 18-59 years of age were invited to enroll in the Breast CFR. In-person interviews were completed for 1,360 (76%) cases; 41 had died before being contacted for interview. After excluding 1) *BRCA1* or *BRCA2* mutation carriers (n=217); 2) cases with a prior history of invasive cancer other than non-melanoma skin cancer (n=362); and 3) and cases with no post-interview follow-up (n=32), 4,153 cases remained in the analyses.

Data Collection

All cases completed a detailed questionnaire on family history of cancer in first- and higher-degree relatives, and a structured questionnaire on established and suspected breast cancer risk factors, including physical activity, height and weight (all prior to diagnosis), as well as treatment. Questionnaires were completed a mean of 19.2 (interquartile range = 10.6-25.2) months after breast cancer diagnosis. Tumor characteristics (tumor size, number of affected lymph nodes, grade (1, 2, 3, missing), histology, estrogen receptor (ER) and progesterone receptor (PR) status) were abstracted from pathology reports. Self-reported height and weight one year prior to diagnosis were used to calculate BMI (kg/m^2), and classified as normal-weight (BMI <25.0 kg/m^2), overweight (BMI=25.0 to 29.9 kg/m^2), and obese (BMI ≥30.0 kg/m^2) [9,22].

Women were asked about their lifetime history of recreational physical activity, including moderate exercise activities or sports (i.e., brisk walking, golf, volleyball, cycling on level streets, recreational tennis, or softball) and strenuous exercise activities or sports (i.e., swimming laps, aerobics, calisthenics, running, jogging, basketball, cycling on hills, or racquetball) at ages 12-17 years, 18-24 years, 25-34 years, 35-44 years, 45-54 years, and ≥55 years, and during the three years prior to diagnosis (recent). For each age interval and each type of activity (moderate and strenuous), information was collected on the duration of activity in hours per week (0.5, 1, 1.5, 2, 3, 4-6, 7-10, ≥11, don't know) and number of months per year (1-3, 4-6, 10-12, don't know). Hours per week and months per year were recoded to the midpoint (the highest hours per week interval was recoded to 15) and multiplied to obtain duration of activity per year (in hours) for each age interval. Lifetime average hours/year of physical activity was obtained by summing the duration of activity per year across the age intervals (except recent physical activity, which was considered separately), and dividing by the number of intervals. Moderate and strenuous activities were weighted by metabolic equivalents (MET) (8.5 for strenuous activity and 5.4 for moderate activity) [23] and combined to obtain MET-hours of physical activity per week. Physical activity was categorized into quartiles for women who exercised, based on the distribution of activity; the reference group for hazard ratio estimation comprised women who did not exercise. In stratified analyses, physical activity was categorized into two groups, based on the median physical activity level for women who exercised. Physical activity was not assessed for Australian cases diagnosed between July 1, 1991 and July 1, 1995 (n=320); thus, they were excluded from analyses of physical activity. For women with information on duration of physical activity for a given age interval, but missing months per year (n=212), the number of months was imputed to six months. Hazard ratio estimates were similar with and without this imputation.

Follow-up

Vital status of cases was ascertained through several follow-up activities, including telephone contact with cases or family members (Australia and Northern California, annually at the latter), annual mailed family history follow-up questionnaires (Ontario), as well as linkage to cancer registry and death registry records, review of medical records, or contact with physicians' offices (all centers). Dates of last follow-up ranged from January 31, 1994 to July 18, 2007, with a median post-interview follow-up of 6.5 years and total follow-up of 24,745 person-years. For the 4,153 cases in this study, 725 deaths were identified (187 in Northern California, 255 in Ontario, and 283 in Australia). Cause of death was not available for these analyses. For the subgroup of cases with physical activity data (n=3,833), 623 deaths were identified.

Statistical Analysis

Multivariable Cox proportional hazards regression was used to analyze associations between all-cause mortality and physical activity and BMI. Days since diagnosis was used as the time scale, with follow-up time left-truncated at the date of interview to avoid potential survival bias. Cases were censored at the date of death or date of last known contact. Relative risks of all-cause mortality were estimated as hazard ratios (HR) with 95% confidence intervals (CI). Wald tests for trend were used to evaluate associations with increasing physical activity and BMI.

Models included adjustments for study center (Northern California, Ontario, Australia), age at diagnosis (continuous years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic white, non-Hispanic Asian, other, missing), years since last pregnancy (nulliparous, <2, 2-4, ≥5, missing) [24], and tumor characteristics significantly associated with breast cancer mortality in our analyses, including size (≤20 mm, >20 mm, missing), number of affected lymph nodes (0, 1-3, ≥4, missing), grade (1, 2, 3, missing), histology (invasive ductal, invasive lobular, other, missing), ER status (negative, positive, missing), and PR status (negative, positive, missing). Secondary analyses were performed with additional adjustment for treatment with chemotherapy (yes, no, missing) and tamoxifen (yes, no, missing) and exclusion of cases diagnosed with evidence of distant metastatic disease. Other characteristics, such as level of education, parity, age at first birth, and radiation treatment (after consideration of other treatment variables) were not associated with all-cause mortality, and therefore were not included in the final multivariable model. The proportional hazards assumption was tested for physical activity and BMI using significance tests of interactions with the time scale, and visual examination of scaled Schoenfeld residual plots; there was no evidence that these variables violated the assumption of proportional hazards.

We performed stratified analyses according to study center, age at diagnosis (<50 or ≥50 years), race/ethnicity, tumor size, number of affected lymph nodes, tumor grade, tumor histology, ER status, PR status, distant metastatic disease at diagnosis, and family history of breast cancer in first-degree relatives. Tests for heterogeneity across strata were conducted using likelihood ratio tests comparing models with and without an interaction term between physical activity or BMI and the stratified variable. *P*-values ≤0.05 were considered statistically significant, and all tests of significance were two-sided. Analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC).

Results

The distributions of lifetime and recent physical activity and BMI are presented in Table 1, along with other personal and tumor characteristics of the cases. On average, women

exercised moderately or vigorously 22.4 MET-hours per week over their lifetime (prior to diagnosis) and 28.9 MET-hours per week (equivalent to 5.3 hours of moderate or 3.4 hours of vigorous activity per week) during the three years prior to breast cancer diagnosis. The majority of cases had a BMI in the normal range one year prior to diagnosis (mean for all cases = 25.4 kg/m²), while 26% were overweight and 17% were obese. Over 70% of tumors with known hormone receptor expression status were ER and/or PR positive.

Recent moderate or vigorous physical activity, compared with no activity, was associated with a 23% to 29% reduced risk of all-cause mortality, depending on quartile of activity (Table 2) (multivariate adjusted HR for any versus no activity = 0.73, 95% CI: 0.60-0.89), whereas average lifetime physical activity was not associated with all-cause mortality; in a secondary analyses, we excluded the first three years of follow-up to ensure that physical activity was assessed well before mortality and found that the results were not appreciably different (data not shown).

The inverse association with recent physical activity, however, was limited to women with ER-positive tumors (HR for any versus no activity= 0.66, 95% CI: 0.51-0.89); no association was found for those with ER-negative tumors (HR for any versus no activity= 0.88, 95% CI: 0.60-1.29) (p- heterogeneity = 0.11) (Table 3). For women with ER-positive tumors, associations with recent physical activity did not differ by BMI or race/ethnicity, with similar inverse trends found for Black, Hispanic and Asian women. Results were similar for women with PR-positive tumors (data not shown). For women with ER-positive tumors, there was no evidence that the inverse association between recent physical activity and all-cause mortality varied by age at diagnosis, menopausal status, study center, tumor grade, tumor size, number of affected nodes, histologic type, or family history of breast cancer in a first-degree relative (data not shown).

Compared to normal-weight women, obese (HR= 1.21, 95% CI: 1.00-1.48), but not overweight (HR= 1.16, 95% CI: 0.92-1.45), women had a higher risk of all-cause mortality. The association varied by age at diagnosis (p for heterogeneity=0.03), with positive associations with BMI limited to women diagnosed when aged ≥50 years (Table 4). Moreover, the positive association with BMI in older women was limited to those with ER-positive tumors (Table 4) or those with PR-positive tumors (data not shown). The associations with BMI did not differ by race/ethnicity, but were somewhat stronger for women who exercised >17.7 MET hrs/wk. Adjustment for recent physical activity did not appreciably change these BMI results. There was no evidence that the association with BMI in older women differed by other factors, such as study center, tumor grade, tumor size, number of affected nodes, histologic type, or family history of breast cancer in first-degree relatives (data not shown). For women aged <50 years at diagnosis, the lack of association with BMI (HR=1.07, 95% CI: 0.86, 1.34 for overweight women; HR=1.07, 95% CI: 0.81, 1.41 for obese women; p-trend=0.53) was consistently observed regardless of the ER status of the tumor and other tumor or disease characteristics (data not shown).

Recent physical activity and BMI were considered jointly in women of all ages (Table 5). Compared to women who were active and of normal weight, those who were active but overweight or obese had a 26% increased risk of death. By contrast, women who were inactive, had a 46% increased risk of death, regardless of BMI.

Discussion

In the present study, recent recreational moderate or vigorous physical activity was associated with lower risk of all-cause mortality after diagnosis of ER-positive breast tumors. This finding is consistent with results of other studies [10,13-15] that also reported

stronger inverse associations between physical activity and mortality for women with hormone receptor positive breast tumors. For women with ER-positive tumors, inverse associations did not differ by BMI or race/ethnicity, although the analyses we were limited by small numbers of non-white women. Ours is the second study [15] to report physical activity findings by race/ethnicity and the first to consider Asian women, as most prior studies were limited to white women.

Several prior studies found weak inverse and/or non-significant associations between physical activity one year prior to diagnosis and survival after breast cancer [11,15,17-19,25]. On the other hand, studies that considered physical activity levels after breast cancer diagnosis and treatment found stronger associations [10,12,13,15]. Consistent with two prior reports [11,18], the present study did not find associations of survival after breast cancer diagnosis with average lifetime physical activity prior to diagnosis, suggesting that timing of physical activity is important, with only recent physical activity conferring benefits to overall survival. By contrast, the California Teachers Study cohort, which assessed physical activity at baseline (1995-1996) and breast cancer diagnosis from 1995 to 2004, found that average lifetime physical activity was more strongly associated with overall mortality than physical activity three years prior to the baseline interview, a time period 3 to 12 years prior to breast cancer diagnosis [16].

Of studies that considered physical activity one year prior to diagnosis, one found higher moderate or vigorous recreational physical activity to be associated with a 30% improved overall survival for overweight or obese women [11]. Another study found that at least 5 hours of exercise per week one year prior to diagnosis was associated with a non-significant 20% decrease in risk of death from breast cancer [18]. In a third study, engaging in at least 9 MET-hours per week of recreational physical activity in the year prior to diagnosis was associated with a 31% lower risk of death [15]. While the present study did not measure physical activity levels after diagnosis or treatment, studies that had such measures found reduced risks of all-cause mortality ranging from 29% to 67% for women who engaged in any (64%-67%) [15], ≥ 2.8 MET-hours per week (41%-56%) [12] or ≥ 3.0 (29%-44%) [10,14] MET-hours per week of physical activity compared to women who exercised less. In addition, women with early-stage breast cancer who walked at least 3 hours per week and consumed at least 5 daily servings of fruit and vegetables for an average of 2 years after breast cancer diagnosis had a 44% reduced risk of death [13].

In the present study, we found that being overweight or obese was associated with an increased risk of death for women of all race/ethnicities who were ≥ 50 years of age at breast cancer diagnosis, independent of physical activity. These findings are consistent with those of other studies [5-7,26,27], including those that found stronger associations for postmenopausal women [7,26] or, in agreement with our results, for women with ER-positive tumors [7,28,29]. There are some studies, however, that found associations between higher BMI and reduced survival in premenopausal or younger women [6,8,9,25,29-33].

Improved survival of physically active women may result from reduced exposure to cyclic estrogen and progesterone levels [19], which may have a greater effect on women with hormone-responsive tumors [10], as suggested by our and prior [10,13] results; improvements in insulin resistance or reductions in hyperinsulinemia [10,34]; and consequent increases in sex hormone binding globulin, which reduces estrogen production and bioavailability [35]. The mechanisms by which higher BMI might increase mortality have, like physical activity, been hypothesized to involve higher circulating levels of estrogens [7], insulin and insulin-like growth factors [36-39]. Furthermore, obese women could have a poorer response to treatment because general chemotherapy caps at a body surface area of 2m^2 , and might therefore be insufficient for larger women [7], or obesity

may influence the metabolism or efficacy of drugs used for systematic therapy [31]. Obesity and physical inactivity could also be indicators of other unhealthy lifestyle behaviors or other chronic health problems that reduce survival [8].

Several potential limitations need to be considered when interpreting our results. We assessed self-reported, pre-diagnosis moderate and vigorous recreational physical activity. Therefore, we were not able to assess the contribution of other types of physical activity (e.g., occupational or household-related activity), which might vary by race/ethnicity [40], or the association with physical activity after breast cancer diagnosis. Some data suggest that, for most women, levels of activity after treatment are similar to their pre-diagnostic levels [41,42]. In one study, however, the risk of death from all causes was increased by four-fold for the 22% of women who decreased their physical activity after diagnosis [15]. Recreational physical activity levels reported in the present study were higher than levels reported in prior studies, suggesting that physical activity levels could have been over-estimated. However, except for tumor hormone receptor status, the association between recent physical activity and all-cause mortality did not vary by any patient or disease characteristics considered in this study, including tumor size, grade, or number of affected nodes. Thus, our results suggest that the inverse association was not restricted to women with early-stage, less debilitating disease and are unlikely to be explained by a reduction in physical activity due to prodromal effects among women who subsequently developed more advanced breast cancer. While we cannot rule out misclassification of physical activity levels, either by race/ethnicity [40] or longer time between diagnosis and study enrollment, previous studies have found self-reported lifetime physical activity to be reliable and highly reproducible [43-46]. Any misclassification in our study was probably non-differential, as recall bias was unlikely. Our study outcome was limited to all-cause mortality, preventing us from examining breast cancer specific mortality and other prognostic endpoints. Prior studies of women with breast cancer have found that 48% to 70% of all deaths were due to breast cancer [10,14-16]. We also lacked information on co-morbidities, which could influence all-cause mortality [47-49]. While other studies have found obese women to be more likely to die of causes unrelated to breast cancer [33,50], a study based on earlier follow-up of the Australian Breast CFR case series reported that obese women were at an increased risk for distant recurrence [9], a surrogate for breast cancer-specific survival.

The body size assessment was based on self-reported weight and height one year prior to diagnosis. Although self-reported BMI has been shown to underestimate measured BMI, the correlation between measured and self-reported BMI has been reported to be high [51-53]. While we lacked information on stage at diagnosis, we were able to adjust the analyses for tumor size and number of involved nodes. Furthermore, our findings were similar when we excluded women diagnosed with known distant metastatic disease (n=58). However, due to the time between diagnosis and enrollment, it is possibly that women with more advanced disease, and possibly different activity and weight patterns, were underrepresented in our study.

The strengths of this study include the large number of incident breast cancer cases from three countries, the population-based design, and the availability of clinical and interview data that allowed us to consider types of breast cancer and subgroups of patients. The three Breast CFRs used the same standardized questionnaire, and findings did not differ by study center. Bias due to differential follow-up was minimized by the use of linkages to population-based cancer registries and death registry records to track outcomes of all cases. We adjusted for any survival bias by left-truncating all cases at the time of recruitment. An additional strength was our ability to adjust for treatment, which did not change our findings. Because treatment is strongly correlated with measures of disease extent that were adjusted for in the analyses, we did not include treatment in our final multivariate models.

Findings from this international, population-based study further support the health benefits of maintaining an active lifestyle and normal weight. In addition to being associated with a decrease in women's risk of breast cancer [40,54], recreational moderate and vigorous physical activity during the three years prior to diagnosis of an ER-positive breast cancer was associated with improved all-cause mortality. Furthermore, obesity was associated with increased all-cause mortality for women diagnosed at age ≥ 50 years with ER-positive breast cancer. Our findings suggest that physical activity and BMI exert independent effects on overall mortality after breast cancer diagnosis. Future studies with larger numbers of women of non-white race/ethnicity will be needed to confirm these findings and consider measures of physical activity after breast cancer diagnosis.

Acknowledgments

The authors thank Enid Satariano and Jocelyn Koo (Northern California Cancer Center), Elaine Maloney and Nayana Weerasooriya (Cancer Care Ontario), and Maggie Angelakos, Judi Maskiell and Gillian Dite (University of Melbourne) for their assistance.

Grants and/or financial support: The Breast Cancer Family Registry (Breast CFR) was supported by the National Cancer Institute, National Institutes of Health under RFA CA-95-011 and CA-06-503, and through cooperative agreements with members of the Breast CFR and Principal Investigators. The three registries contributing data to this analysis were supported by U01 CA69417 (Northern California Cancer Center), U01 CA69467 (Cancer Care Ontario), and U01 CA69638 (University of Melbourne). Kelly-Anne Phillips was supported by the Cancer Council Victoria Colebatch Clinical Research Fellowship. The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast CFR, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the Breast CFR.

References

1. Stewart, BW.; Kleihues, P. World Cancer Report. International Agency for Research on Cancer. IARC Press; Lyon: 2003.
2. Sunga AY, Eberl MM, Oeffinger KC, Hudson MM, Mahoney MC. Care of cancer survivors. *Am Fam Physician* 2005;71:699–706. [PubMed: 15742907]
3. Stein KD, Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. *Cancer* 2008;112:2577–2592. [PubMed: 18428205]
4. Geiger AM, Thwin SS, Lash TL, Buist DS, Prout MN, Wei F, Field TS, Ulcickas Yood M, Frost FJ, Enger SM, Silliman RA. Recurrences and second primary breast cancers in older women with initial early-stage disease. *Cancer* 2007;109:966–974. [PubMed: 17243096]
5. Carmichael AR. Obesity as a risk factor for development and poor prognosis of breast cancer. *Bjog* 2006;113:1160–1166. [PubMed: 16945118]
6. Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. *J Clin Oncol* 2002;20:1128–1143. [PubMed: 11844838]
7. Rock CL, Demark-Wahnefried W. Nutrition and survival after the diagnosis of breast cancer: a review of the evidence. *J Clin Oncol* 2002;20:3302–3316. [PubMed: 12149305]
8. Carmichael AR. Obesity and prognosis of breast cancer. *Obes Rev* 2006;7:333–340. [PubMed: 17038127]
9. Loi S, Milne RL, Friedlander ML, McCredie MR, Giles GG, Hopper JL, Phillips KA. Obesity and outcomes in premenopausal and postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev* 2005;14:1686–1691. [PubMed: 16030102]
10. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA* 2005;293:2479–2486. [PubMed: 15914748]
11. Abrahamson PE, Gammon MD, Lund MJ, Britton JA, Marshall SW, Flagg EW, Porter PL, Brinton LA, Eley JW, Coates RJ. Recreational physical activity and survival among young women with breast cancer. *Cancer* 2006;107:1777–1785. [PubMed: 16967443]

12. Holick CN, Newcomb PA, Trentham-Dietz A, Titus-Ernstoff L, Bersch AJ, Stampfer MJ, Baron JA, Egan KM, Willett WC. Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev* 2008;17:379–386. [PubMed: 18250341]
13. Pierce JP, Stefanick ML, Flatt SW, Natarajan L, Sternfeld B, Madlensky L, Al-Delaimy WK, Thomson CA, Kealey S, Hajek R, Parker BA, Newman VA, Caan B, Rock CL. Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. *J Clin Oncol* 2007;25:2345–2351. [PubMed: 17557947]
14. Sternfeld B, Weltzien E, Quesenberry CP Jr, Castillo AL, Kwan M, Slattery ML, Caan BJ. Physical activity and risk of recurrence and mortality in breast cancer survivors: findings from the LACE study. *Cancer Epidemiol Biomarkers Prev* 2009;18:87–95. [PubMed: 19124485]
15. Irwin ML, Smith AW, McTiernan A, Ballard-Barbash R, Cronin K, Gilliland FD, Baumgartner RN, Baumgartner KB, Bernstein L. Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. *J Clin Oncol* 2008;26:3958–3964. [PubMed: 18711185]
16. West-Wright CN, Henderson KD, Sullivan-Halley J, Ursin G, Deapen D, Neuhausen S, Reynolds P, Chang E, Ma H, Bernstein L. Long-Term and Recent Recreational Physical Activity and Survival After Breast Cancer: The California Teachers Study. *Cancer Epidemiol Biomarkers Prev*. 2009 1055-9965.EPI-09-0538 [pii]. 10.1158/1055-9965.EPI-09-0538
17. Borugian MJ, Sheps SB, Kim-Sing C, Van Patten C, Potter JD, Dunn B, Gallagher RP, Hislop TG. Insulin, macronutrient intake, and physical activity: are potential indicators of insulin resistance associated with mortality from breast cancer? *Cancer Epidemiol Biomarkers Prev* 2004;13:1163–1172. [PubMed: 15247127]
18. Enger SM, Bernstein L. Exercise activity, body size and premenopausal breast cancer survival. *Br J Cancer* 2004;90:2138–2141. [PubMed: 15150561]
19. Rohan TE, Fu W, Hiller JE. Physical activity and survival from breast cancer. *Eur J Cancer Prev* 1995;4:419–424. [PubMed: 7496329]
20. John EM, Hopper JL, Beck JC, Knight JA, Neuhausen SL, Senie RT, Ziogas A, Andrulis IL, Anton-Culver H, Boyd N, Buys SS, Daly MB, O'Malley FP, Santella RM, Southey MC, Venne VL, Venter DJ, West DW, Whittemore AS, Seminara D. The Breast Cancer Family Registry: an infrastructure for cooperative multinational, interdisciplinary and translational studies of the genetic epidemiology of breast cancer. *Breast Cancer Res* 2004;6:R375–389. Epub 2004 May 2019. [PubMed: 15217505]
21. Chang ET, Milne RL, Phillips KA, Figueiredo JC, Sangaramoorthy M, Keegan TH, Andrulis IL, Hopper JL, Goodwin PJ, O'Malley FP, Weerasooriya N, Apicella C, Southey MC, Friedlander ML, Giles GG, Whittemore AS, West DW, John EM. Family history of breast cancer and all-cause mortality after breast cancer diagnosis in the Breast Cancer Family Registry. *Breast Cancer Res Treat*. 2008
22. Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. *Lancet Oncol* 2002;3:565–574. [PubMed: 12217794]
23. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000;32:S498–504. [PubMed: 10993420]
24. Phillips KA, Milne RL, West DW, Goodwin PJ, Giles GG, Chang ET, Figueiredo JC, Friedlander ML, Keegan TH, Glendon G, Apicella C, O'Malley FP, Southey MC, Andrulis IL, John EM, Hopper JL. Prediagnosis reproductive factors and all-cause mortality for women with breast cancer in the breast cancer family registry. *Cancer Epidemiol Biomarkers Prev* 2009;18:1792–1797. [PubMed: 19505912]
25. Dal Maso L, Zucchetto A, Talamini R, Serraino D, Stocco CF, Vercelli M, Falcini F, Franceschi S. Effect of obesity and other lifestyle factors on mortality in women with breast cancer. *Int J Cancer* 2008;123:2188–2194. [PubMed: 18711698]
26. Tao MH, Shu XO, Ruan ZX, Gao YT, Zheng W. Association of overweight with breast cancer survival. *Am J Epidemiol* 2006;163:101–107. Epub 2005 Dec 2007. [PubMed: 16339054]

27. Barnett GC, Shah M, Redman K, Easton DF, Ponder BA, Pharoah PD. Risk factors for the incidence of breast cancer: do they affect survival from the disease? *J Clin Oncol* 2008;26:3310–3316. [PubMed: 18612147]
28. Maehle BO, Tretli S. Pre-morbid body-mass-index in breast cancer: reversed effect on survival in hormone receptor negative patients. *Breast Cancer Res Treat* 1996;41:123–130. [PubMed: 8944330]
29. Majed B, Moreau T, Senouci K, Salmon RJ, Fourquet A, Asselain B. Is obesity an independent prognosis factor in woman breast cancer? *Breast Cancer Res Treat* 2008;111:329–342. [PubMed: 17939036]
30. Daling JR, Malone KE, Doody DR, Johnson LG, Gralow JR, Porter PL. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. *Cancer* 2001;92:720–729. [PubMed: 11550140]
31. Whiteman MK, Hillis SD, Curtis KM, McDonald JA, Wingo PA, Marchbanks PA. Body mass and mortality after breast cancer diagnosis. *Cancer Epidemiol Biomarkers Prev* 2005;14:2009–2014. [PubMed: 16103453]
32. Abrahamson PE, Gammon MD, Lund MJ, Flagg EW, Porter PL, Stevens J, Swanson CA, Brinton LA, Eley JW, Coates RJ. General and abdominal obesity and survival among young women with breast cancer. *Cancer Epidemiol Biomarkers Prev* 2006;15:1871–1877. [PubMed: 17035393]
33. Berclaz G, Li S, Price KN, Coates AS, Castiglione-Gertsch M, Rudenstam CM, Holmberg SB, Lindtner J, Erien D, Collins J, Snyder R, Thurlimann B, Fey MF, Mendiola C, Werner ID, Simoncini E, Crivellari D, Gelber RD, Goldhirsch A. Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience. *Ann Oncol* 2004;15:875–884. [PubMed: 15151943]
34. Ligibel JA, Campbell N, Partridge A, Chen WY, Salinardi T, Chen H, Adloff K, Keshaviah A, Winer EP. Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. *J Clin Oncol* 2008;26:907–912. [PubMed: 18281663]
35. Bianchini F, Kaaks R, Vainio H. Weight control and physical activity in cancer prevention. *Obes Rev* 2002;3:5–8. [PubMed: 12119660]
36. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, Hartwick W, Hoffman B, Hood N. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol* 2002;20:42–51. [PubMed: 11773152]
37. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Hartwick W, Hoffma B, Hood N. Insulin-like growth factor binding proteins 1 and 3 and breast cancer outcomes. *Breast Cancer Res Treat* 2002;74:65–76. [PubMed: 12150454]
38. Del Giudice ME, Fantus IG, Ezzat S, McKeown-Eyssen G, Page D, Goodwin PJ. Insulin and related factors in premenopausal breast cancer risk. *Breast Cancer Res Treat* 1998;47:111–120. [PubMed: 9497099]
39. Suga K, Imai K, Eguchi H, Hayashi S, Higashi Y, Nakachi K. Molecular significance of excess body weight in postmenopausal breast cancer patients, in relation to expression of insulin-like growth factor I receptor and insulin-like growth factor II genes. *Jpn J Cancer Res* 2001;92:127–134. [PubMed: 11223541]
40. John EM, Horn-Ross PL, Koo J. Lifetime physical activity and breast cancer risk in a multiethnic population: the San Francisco Bay area breast cancer study. *Cancer Epidemiol Biomarkers Prev* 2003;12:1143–1152. [PubMed: 14652273]
41. Rhodes RE, Courneya KS, Bobick TM. Personality and exercise participation across the breast cancer experience. *Psychooncology* 2001;10:380–388. [PubMed: 11536416]
42. Courneya KS, Friedenreich CM. Relationship between exercise during treatment and current quality of life among survivors of breast cancer. *J Psychosom Oncol* 1997;15:35–57.
43. 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;86:1403–1408. [PubMed: 8072034]
44. Chasan-Taber L, Erickson JB, McBride JW, Nasca PC, Chasan-Taber S, Freedson PS. Reproducibility of a self-administered lifetime physical activity questionnaire among female college alumnae. *Am J Epidemiol* 2002;155:282–289. [PubMed: 11821254]

45. Kriska AM, Knowler WC, LaPorte RE, Drash AL, Wing RR, Blair SN, Bennett PH, Kuller LH. Development of questionnaire to examine relationship of physical activity and diabetes in Pima Indians. *Diabetes Care* 1990;13:401–411. [PubMed: 2318100]
46. Kriska AM, Sandler RB, Cauley JA, LaPorte RE, Hom DL, Pambianco G. The assessment of historical physical activity and its relation to adult bone parameters. *Am J Epidemiol* 1988;127:1053–1063. [PubMed: 3358406]
47. Satariano WA. Aging, comorbidity, and breast cancer survival: an epidemiologic view. *Adv Exp Med Biol* 1993;330:1–11. [PubMed: 8368127]
48. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. *Ann Intern Med* 1994;120:104–110. [PubMed: 8256968]
49. Tammemagi CM, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D. Comorbidity and survival disparities among black and white patients with breast cancer. *Jama* 2005;294:1765–1772. [PubMed: 16219879]
50. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;348:1625–1638. [PubMed: 12711737]
51. Ezzati M, Martin H, Skjold S, Vander Hoorn S, Murray CJ. Trends in national and state-level obesity in the USA after correction for self-report bias: analysis of health surveys. *J R Soc Med* 2006;99:250–257. [PubMed: 16672759]
52. Villanueva EV. The validity of self-reported weight in US adults: a population based cross-sectional study. *BMC Public Health* 2001;1:11. Epub 2001 Nov 2006. [PubMed: 11716792]
53. Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. *Public Health Nutr* 2002;5:561–565. [PubMed: 12186665]
54. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. *Br J Sports Med* 2008;42:636–647. [PubMed: 18487249]

Table 1
Distribution of personal and tumor characteristics of cases (N=4,153)

Characteristic	N	%
Breast Cancer Family Registry		
Ontario, Canada	1578	38
Northern California, USA	1306	31
Melbourne and Sydney, Australia	1269	31
Age at diagnosis (years)		
<35	542	13
35-39	578	14
40-44	558	13
45-49	776	19
50-54	784	19
55-59	474	11
≥60	441	11
Race/ethnicity		
Non Hispanic white	3133	75
Non-Hispanic Black	209	5
Hispanic white	221	5
Non-Hispanic Asian	452	11
Other	79	2
Missing	59	1
Time since last full term pregnancy (years)		
Nulliparous	920	22
<2	174	4
2-4	309	7
≥5	2743	66
Missing	7	<1
Number of affected lymph nodes		
None	2242	54
1-3	976	23
≥4	495	12
Missing	440	11
Tumor size (mm)		
≤20	2579	62
>20	1303	31
Missing	271	7
Tumor grade		
1	788	19
2	1518	36
3	1522	37
Missing	325	8

Characteristic	N	%
Histologic type		
Ductal	3402	82
Lobular	245	6
Other	296	7
Missing	210	5
Estrogen receptor status		
Negative	1002	24
Positive	2717	65
Missing	434	11
Progesterone receptor status		
Negative	1094	26
Positive	2602	63
Missing	457	11
Chemotherapy		
No	1404	34
Yes	2024	49
Missing	725	18
Tamoxifen		
No	1945	47
Yes	1623	39
Missing	585	14
BMI (kg/m ²)		
<25.0	2220	53
25.0-29.9	1094	26
≥30.0	712	17
Missing	127	3
Recent ^a Physical Activity (MET-hrs/wk)		
Mean	22.4	
Standard Deviation	28.2	
Missing (N)	110	
Not assessed (N)	320	
Lifetime ^b Physical Activity(MET-hrs/wk)		
Mean	28.9	
Standard Deviation	28.6	
Missing (N)	73	
Not assessed (N)	320	

^aRecent activity during the 3 years before diagnosis.

^bLifetime activity from age 12 to age at reference year, not including recent activity during the 3 years before diagnosis.

Table 2
Associations of physical activity with overall survival: estimated hazard ratios (HR) with 95% confidence intervals (CI) (N=3,833)

Physical Activity	Deaths N=623	HR ^a (95% CI)	HR ^b (95% CI)
Recent ^c Physical Activity (MET ^d hrs/wk)			
0	140	1.00	1.00
Q1: ≤ 9.9	143	0.72 (0.57-0.92)	0.71 (0.56-0.90)
Q2: 10.0-17.7	100	0.71 (0.55-0.93)	0.73 (0.56-0.95)
Q3: 17.8-38.2	110	0.64 (0.49-0.82)	0.72 (0.56-0.93)
Q4: > 38.2	112	0.67 (0.52-0.87)	0.77 (0.60-1.00)
Missing	18	p trend ^e < 0.01	p trend ^e = 0.10
Lifetime ^f Physical Activity (MET ^d hrs/wk)			
Q1: ≤ 6.7	129	1.00	1.00
Q2: 6.8-16.3	120	0.82 (0.64-1.06)	0.86 (0.67-1.11)
Q3: 16.4-26.1	113	0.80 (0.61-1.04)	0.84 (0.64-1.10)
Q4: 26.2-46.0	121	0.83 (0.64-1.07)	0.88 (0.68-1.14)
Q5: > 46.0	128	0.88 (0.68-1.14)	0.93 (0.72-1.21)
Missing	12	p trend ^e = 0.46	p trend ^e = 0.74

^a Adjusted for study center (Ontario, Northern California, Australia), age of diagnosis (continuous), and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic white, non-Hispanic Asian, other, missing).

^b Adjusted for study center (Ontario, Northern California, Australia), age of diagnosis (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic Asian, other, missing), number of affected nodes (0, 1-3, 4+, missing), BMI (<25.0, 25.0-29.9, ≥30.0, missing), time since last full term pregnancy (nulliparous, <2 yrs, 2-4 yrs, ≥5 yrs, missing), ER status (negative, positive, missing), PR status (negative, positive, missing), tumor grade (1,2,3, missing), tumor size (≤20, >20, missing), and tumor type (invasive ductal, invasive lobular, other, missing).

^c Recent activity during the 3 years before diagnosis.

^d Average metabolic equivalent hours weighted 8.5 for strenuous activity and 5.4 for moderate activity.

^e Excludes missing physical activity.

^f Lifetime activity from age 12 to age at reference year, not including recent activity during the 3 years before diagnosis.

Table 3
Associations of recent physical activity with overall survival: estimated hazard ratios (HR) with 95% confidence intervals (CI), stratified by estrogen receptor (ER) status (N=3,833)

Patient or tumor characteristic	Recent ^a physical activity (MET ^b hrs/wk)	Deaths (N)	HR ^c (95% CI)	p heterogeneity ^d
Estrogen receptor status ^e				
Positive (n = 2553)	0	87	1.00	0.11
	Q1: ≤ 9.9	85	0.69 (0.51-0.95)	
	Q2: 10.0-17.7	56	0.70 (0.49-1.00)	
	Q3: 17.8-38.2	56	0.58 (0.41-0.82)	
	Q4: > 38.2	60	0.67 (0.48-0.94)	
			p trend ^f = 0.01	
	Missing	8		
Negative (n = 881)	0	36	1.00	
	Q1: ≤ 9.9	38	0.74 (0.46-1.18)	
	Q2: 10.0-17.7	35	0.80 (0.49-1.31)	
	Q3: 17.8-38.2	45	1.00 (0.63-1.58)	
	Q4: > 38.2	44	1.05 (0.66-1.68)	
			p trend ^f = 0.35	
	Missing	4		
Estrogen receptor positive				
Race/ethnicity ^g				
Non-Hispanic white (n = 1922)	0	60	1.00	
	M1: ≤ 17.7	111	0.69 (0.50-0.96)	
	M2: > 17.7	98	0.65 (0.47-0.92)	
			p trend ^f = 0.03	
	Missing	5		
Non-Hispanic black (n = 131)	0	3	1.00	
	M1: ≤ 17.7	10	0.72 (0.12-4.22)	
	M2: > 17.7	4	0.72 (0.08-6.98)	
			p trend ^f = 0.82	
	Missing	2		
Hispanic (n = 148)	0	9	1.00	
	M1: ≤ 17.7	6	0.33 (0.07-1.53)	
	M2: > 17.7	6	0.48 (0.13-1.79)	
			p trend ^f = 0.33	
	Missing	0		
Non-Hispanic Asian (n = 300)	0	11	1.00	
	M1: ≤ 17.7	11	1.05 (0.41-2.73)	
	M2: > 17.7	8	0.77 (0.28-2.13)	
			p trend ^f = 0.64	
	Missing			

Patient or tumor characteristic	Recent ^a physical activity (MET ^b hrs/wk)	Deaths (N)	HR ^c (95% CI)	p heterogeneity ^d
	Missing	0		0.97
Body Mass Index ^h (kg/m ²)				
<25.0 (n = 1392)	0	38	1.00	
	M1: ≤ 17.7	67	0.75 (0.49-1.14)	
	M2: > 17.7	61	0.65 (0.42-1.00)	
			p trend ^f = 0.06	
	Missing	4		
25.0-29.9 (n = 656)	0	26	1.00	
	M1: ≤ 17.7	35	0.59 (0.35-1.01)	
	M2: > 17.7	38	0.77 (0.45-1.31)	
			p trend ^f = 0.51	
	Missing	0		
≥30.0 (n = 423)	0	18	1.00	
	M1: ≤ 17.7	30	0.92 (0.49-1.73)	
	M2: > 17.7	15	0.74 (0.36-1.55)	
			p trend ^f = 0.43	
	Missing	3		0.59

^aRecent activity during the 3 years before diagnosis.

^bAverage metabolic equivalent (MET) hours weighted 8.5 for strenuous and 5.4 for moderate activity.

^cAdjusted for Breast Cancer Family Registry (Ontario, Northern California, Australia), age of diagnosis (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic Asian, other, missing), number of affected nodes (0, 1-3, 4+, missing), BMI (<25.0, 25.0-29.9, ≥30.0, missing), years since last full term pregnancy (nulliparous, <2, 2-4, ≥5), ER status (negative, positive, missing), PR status (negative, positive, missing), tumor grade (1,2,3, missing), tumor size (≤20, >20, missing), and tumor type (invasive ductal, invasive lobular, other, missing).

^dFrom Likelihood Ratio Test.

^eExcludes 399 cases with missing ER status; adjusted for all variables^c, except ER status.

^fExcludes missing physical activity.

^gExcludes 52 cases of other or missing race/ethnicity; adjusted for all variables^c, except race/ethnicity.

^hExcludes 82 cases with missing BMI; adjusted for all variables^c, except BMI.

Table 4
Stratified associations of body mass index with overall survival for women aged ≥ 50 years at diagnosis: estimated hazard ratios (HR) with 95% confidence intervals (CI) (N=1,699)

Patient or tumor characteristic	Body mass index (kg/m ²)	Deaths (N)	HR ^a (95% CI)	p heterogeneity ^b
Overall (n = 1 699)	<25.0	83	1.00	
	25.0-29.9	73	1.43 (1.04-1.99)	
	≥ 30.0	66	1.56 (1.10-2.21)	
	Missing	10	p trend ^c = 0.01	
Estrogen receptor status ^d				
Positive (n = 1206)	<25.0	49	1.00	
	25.0-29.9	42	1.39 (0.90-2.15)	
	≥ 30.0	39	1.77 (1.11-2.82)	
	Missing	9	p trend ^c = 0.01	
Negative (n = 301)	<25.0	22	1.00	
	25.0-29.9	24	1.47 (0.75-2.88)	
	≥ 30.0	17	1.04 (0.49-2.19)	
	Missing	0	p trend ^c = 0.86	0.17
Estrogen receptor positive status				
Race/ethnicity ^e				
Non-Hispanic white (n=927)	<25.0	36	1.00	
	25.0-29.9	34	1.70 (1.04-2.79)	
	≥ 30.0	30	2.41 (1.42-4.10)	
	Missing	8	p trend ^c < 0.01	
Non-White (n=274)	<25.0	13	1.00	
	25.0-29.9	7	1.03 (0.35-3.04)	
	≥ 30.0	9	1.52 (0.57-4.04)	

Patient or tumor characteristic	Body mass index (kg/m ²)	Deaths (N)	HR ^a (95% CI)	p heterogeneity ^b
Recent ^f physical activity ^g (MET ^h hrs/wk)	Missing	1	p trend ^c = 0.42	
				0.28
	None (n=233)			
	<25.0	15	1.00	
≤ 17.7 (n=470)	25.0-29.9	8	0.56 (0.19-1.71)	
	≥30.0	15	1.57 (0.64-3.85)	
			p trend ^c = 0.29	
	Missing	3		
> 17.7 (n=456)	<25.0	19	1.00	
	25.0-29.9	17	1.28 (0.64-2.55)	
	≥30.0	14	1.32 (0.61-2.85)	
			p trend ^c = 0.42	
	Missing	6		
	<25.0	12	1.00	
	25.0-29.9	16	2.99 (1.36-6.55)	
	≥30.0	8	3.12 (1.15-8.49)	
	Missing	0	p trend ^c = 0.01	0.10

^a Adjusted for Breast Cancer Family Registry (Ontario, Northern California, Australia), age of diagnosis (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic Asian, other, missing), time since last full term pregnancy (nulliparous, <2yrs, 2-4yrs, ≥5yrs, missing), number of affected nodes (0, 1-3, 4+, missing), ER status (negative, positive, missing), PR status (negative, positive, missing), tumor grade (1,2,3, missing), tumor size (≤20, >20, missing), tumor type (invasive ductal, invasive lobular, other, missing), and recent physical activity (0, ≤17.7, >17.7 MET hrs/wk).

^b From Likelihood Ratio Test.

^c Excludes missing BML.

^d Excludes 192 cases with missing ER status; adjusted for all variables^a, except ER status.

^e Excludes 5 cases with other or missing race/ethnicity; adjusted for all variables^a, except ER status and race/ethnicity.

^f Recent activity during the 3 years before diagnosis.

^g Excludes 44 cases with missing recent physical activity; adjusted for all variables^a, except ER status and recent physical activity.

^h Average metabolic equivalent (MET) hours weighted 8.5 for strenuous and 5.4 for moderate activity.

Table 5
Joint associations of body mass index and recent physical activity with overall survival: estimated hazard ratios (HR) with 95% confidence intervals (CI) (N=3,833)

	Recent ^a physical activity ^b (MET ^c hrs/wk)				p heterogeneity ^f
	Active (>0)		Sedentary (0)		
	Deaths (N)	HR ^e (95% CI)	Deaths (N)	HR ^e (95% CI)	
Body mass index ^d (kg/m ²)					
< 25.0	234	1.00	64	1.46 (1.10-1.94)	
≥ 25.0	213	1.26 (1.04-1.52)	67	1.46 (1.10-1.93)	0.26

^aRecent activity during the 3 years before diagnosis.

^bExcludes 110 cases with missing recent physical activity.

^cAverage metabolic equivalent (MET) hours weighted 8.5 for strenuous and 5.4 for moderate activity.

^dExcludes 124 cases with missing BMI.

^eAdjusted for Breast Cancer Family Registry (Ontario, Northern California, Australia), age of diagnosis (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic Asian, other, missing), time since last full term pregnancy (nulliparous, <2yrs, 2-4yrs, ≥5yrs, missing), number of affected nodes (0, 1-3, 4+, missing), ER status (negative, positive, missing), PR status (negative, positive, missing), tumor grade (1,2,3, missing), tumor size (≤20, >20, missing), and tumor type (invasive ductal, invasive lobular, other, missing).

^fFrom Likelihood Ratio Test.